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13. ABSTRACT *(Maximum 200* The second year of work towards the completion of a doctoral degree, focused on breast cancer epidemiology, at the University of Texas School of Public Health, Houston, Texas has been completed. Analyzed data are a subset of that collected for the study, 'Breast Cancer Epidemiology in NM Hispanic Women'. The Principal Investigator of this training grant served as Project Director of this study conducted by the Epidemiology and Cancer Control Program at the University of New Mexico. This statewide, population-based case-control study includes 712 cases and 844 controls. Incident cases (01/01/92 - 12/31/94) were ascertained through the New Mexico Tumor Registry. Controls were frequency matched on health planning district, ethnicity, and age-group.The data collected included demographics, reproductive and medical history, medication usage, cigarette usage and alcohol consumption, and diet. The doctoral dissertation focuses on alcohol as a risk factor for all women, and for Hispanic and non-Hispanic white women, adjusting for potential confounders. 'Past' alcohol consumption is based on history of alcohol intake at ages 25, 35, and 50, and 'recent' intake on a food frequency questionnaire. Hormone receptor status is also investigated.

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Kathy B. Baumgartner 9/27/98

PI - Signature Date

TABLE OF CONTENTS

Table of Contents (continued)

INTRODUCTION

The focus of this predoctoral fellowship training grant, *"Dietary Intake, Alcohol Consumption, and Menopausal Status: A Comparison of Hispanic and non-Hispanic Women"* and doctoral dissertation, is on alcohol and its association with other risk factors for breast cancer. The basic hypothesis is that alcohol, based on evidence from other studies, may be important in the increasing rates of breast cancer. The second year of grant work on the predoctoral fellowship training grant focused on library research, the submission and completion of the formal dissertation proposal to the University of Texas School of Public Health, Houston, Texas (UTSPH), and the initiation of data analysis. The scope of the dissertation was narrowed to alcohol consumption, excluding diet in general, based on the recommendation of the doctoral thesis committee. However, total energy intake and total fat will be evaluated as potential confounders in the analyses of 'recent' alcohol intake. The specific aims and background sections are based on the dissertation proposal, but the present report includes more detailed information. The final dissertation proposal submitted to UTSPH is provided in Appendix A-1.

The following report details: (1) the significance of this research and the specific aims and hypotheses; (2) a background review of previous studies on alcohol consumption and breast cancer including, hormone receptor status of breast tumors, and studies of Hispanic ethnicity and breast cancer risk; (3) materials and methods, including selection of cases and controls, and data collection; (4) statistical methods, including the measurement of alcohol exposure variables, hormone receptor status, and confounding variables, and data analysis; (5) results; and (6) discussion including the findings to date, and statement of work related to each of the three years covered under this grant.

SPECIFIC AIMS

The incidence of breast cancer in Hispanic women has been documented to be lower than in non-Hispanic white women residing in the West and Southwest (1, 2). In New Mexico, incidence and mortality rates have increased rapidly among Hispanic women since the late 1950s, especially in the younger age-groups, although prevalence rates for Hispanic women are intermediate to those for American Indians and non-

Hispanic white women (1-4). Incidence rates increased by 56% over a 19-year period, and mortality increased by almost 100% over the 30-year period 1958-1987 (3). Incidence rates reported for Hispanic women *vs.* non-Hispanic white women range from 58/100,000 *vs.* 112/100,000 for the time-period 1983 to 1987 in New Mexico (3), to 69.8 *vs.* 115.7 for the time-period 1988 to 1992 for Surveillance, Epidemiology and End Results (SEER) data (5).

The proposed study provides an opportunity to further research on the primary cancer for Hispanic women (6). It is projected that Hispanics will represent the largest ethnic group in the US population by the year 2000, and account for approximately 17% of the total U.S. population by the year 2030 (7). New Mexico has the largest percentage of Hispanics (40%) to total state population in the United States (7), and has a statewide cancer registry, the New Mexico Tumor Registry (NMTR), as a part of the SEER Program of the National Cancer Institute. There are 11 SEER geographic areas covering approximately 14% of the US population. This includes 25% of the Hispanic population. The majority of the Hispanic population in the SEER coverage area resides in Los Angeles (60%), New Mexico (10%), San Francisco and San Jose/Monterey (9%), and Connecticut (4%) (5).

Although breast cancer incidence rates and mortality rates have increased among Hispanic women, the causes of breast cancer in this minority population have not been adequately characterized. There are few data available on breast cancer risk factors for Hispanic women (3, 4, 8-10), and in particular, insufficient understanding of dietary and alcohol practices (11). New Mexican Hispanic women, especially over age 50, are reported to have lower alcohol intake, and are more likely to be non-drinkers than non-Hispanic white women (12). One study has reported that alcohol intake was associated with a nonsignificant increased breast cancer risk for Hispanic women (13). Otherwise, the association of alcohol consumption with breast cancer risk has not been investigated in Hispanic women.

The purpose of this study is to evaluate the primary hypothesis that alcohol consumption is associated with increased breast cancer risk among Hispanic and non-Hispanic white women using data from a population-based case-control study, the 'New

Mexico Women's Health Study'. The proposed study will result in publishable work on this association for Hispanic and non-Hispanic white women residing in New Mexico. The primary hypotheses are detailed below.

H_{1A}: The risk of breast cancer for women who consume alcohol is higher than for those who do not consume alcohol, after adjustment for other dietary and nondietary risk factors.

H_{1B}: The risk of breast cancer for Hispanic women who consume alcohol is higher than for non-Hispanic white women who consume alcohol, after adjustment for covariates.

H_{2A}: The risk of hormone receptor-negative breast cancer for women who consume alcohol is higher than for those who do not consume alcohol, after adjustment for covariates.

H_{2B}: The risk of hormone receptor-negative breast cancer for Hispanic women who consume alcohol is higher than for non-Hispanic white women who consume alcohol, after adjustment for covariates.

In order to investigate these hypotheses the following specific aims will be completed.

1. To estimate the risk of breast cancer for women who consume alcohol. The weight of evidence has consistently shown an increased risk of breast cancer with alcohol consumption, defined by both a modest and high intake, among both pre- and postmenopausal women (14-16). Risk has been on the order of a 30% to 70% increase. Alcohol consumption as a main effect will be evaluated in terms of both recent and past intake, in addition to lifetime exposure. All three measures have been reported to increase risk of breast cancer (13, 14, 16, 17), although overall, the evidence suggests that alcohol may be more important as a late-stage promoter for breast cancer risk, suggesting a stronger contribution to risk from recent intake (14, 16, 18). Variable distributions and univariate analyses will be conducted prior to the modeling stage. Potential confounders will be included in the fully adjusted model. The dependent variable, independent alcohol-related exposure variables, and potential confounders are discussed under the 'Materials and Methods' section.

2. To estimate the risk of breast cancer for Hispanic and non-Hispanic white women for alcohol consumption. Studies have primarily included non-Hispanic white women. Only one study of alcohol consumption and breast cancer risk has included Hispanic ethnicity as a risk factor (13). Results for average lifetime alcohol intake indicated a 24% (0.70-2.19) increase in risk per 13 grams(g)/day. This study was limited to postmenopausal women in Los Angeles, and the sample size by ethnicity was not included. The proposed study will determine whether the risk of breast cancer varies when stratified by ethnicity for both univariate and multivariate conditional logistic regression adjusting for confounders.

3. To estimate the risk of hormone receptor breast cancer for alcohol consumption. Hormone receptor status appears to be related to prognosis and survival, and possibly to etiology (19, 20). It has offered an additional insight into associations of certain risk factors (i.e. alcohol, dietary fat, parity, body mass index) and breast cancer (21-24). Some studies (21-23) have shown an association between alcohol consumption and hormone receptor status, variously defined as a single estrogen receptor (ER) measure, progesterone (PR) measure, and the joint combination of ER/PR status. In the cohort 'Iowa Women's Health Study', an increase in risk for ER-/PR- breast tumors was reported for postmenopausal women for 'ever' use of alcohol (RR=1.37, 95%CI 0.86-2.18) (23). This risk increased for women who were in the highest alcohol intake group, and also on estrogen replacement therapy, or had a family history of breast cancer, or who were obese (22). In contrast, a case-control study of Japanese women, aged 25 years and older, failed to find an association between alcohol consumption and joint hormone receptor status (25). However, alcohol exposure was measured dichotomously as 'ever' *vs.* 'never' use, and only 40% of cases had known receptor status. In this analysis, the dependent variable will be categorized as a polychotomous nominal variable based on hormone receptor type of breast cancer (ER+PR+, ER+PR-, ER-PR+, ER-PR-, ERPR unknown). Analyses will follow the same procedure as noted under specific aim one. The number of categories for the dependent variable will depend on receptor type sample sizes. If there appears to be little difference between the subtypes ER+PR+, ER+PR-,

ER-PR+, these categories may be collapsed in order to increase power for testing the hypothesis that risk is specifically increased for ER-PR- status.

4. To estimate the risk of hormone receptor breast cancer for Hispanic and non-Hispanic white women for alcohol consumption. To date, there are no studies investigating the presence of a differential risk for hormone receptor breast cancer subtypes and alcohol consumption by ethnicity. Results, based on the large 'Patient Care Evaluation Studies of Breast Cancer' investigation of women 20 to 79 years of age, showed no difference between Hispanic and non-Hispanic white ethnicity for ER/PR status, when ER+PR+ breast cancer cases were compared with ER+PR-, ER-PR+, or ER-PR- cases (26). However, this was a case-case breast cancer study, and the analysis included only 236 Hispanic women out of a total of 410. Risk estimates for hormone receptor-specific breast cancer associated with alcohol consumption will be calculated and stratified by ethnicity, while adjusting for other covariates.

BACKGROUND - PREVIOUS STUDIES

Alcohol Consumption

Alcohol consumption is a common exposure. Recent statistics provide figures reporting that 61% of women over the age of 18 are current consumers of alcohol (12 or more drinks per year) (27). Of these women, 39.4% reported their usage as light (≤ 3 drinks/week), 27.4% as moderate (4-13 drinks/week), and 9.1% as heavy (14+ drinks/week). Alcohol, as an important component of dietary intake, is subject to modification more easily than the established reproductive risk factors. The following figures of alcohol consumption are provided by selected studies to provide some idea of the prevalence of alcohol consumption among women with breast cancer compared to those without breast cancer.

	Percent Ever Drinkers	
Case-Control Studies	**Cases**	**Controls**
Toniolo et al. (1989) (28)/Italy	72	63
	[15]	**[7.4]**
Rosenberg et al. (1990) (29)/US	70	74
Howe et al. (1991) (30)/US	67	69
	[5]	**[3.6]**
Friedenreich et al.(1993) (31)/Canada		77 76
	[8]	**[6.8]**
Swanson et al. (1997) (14)/US	65	62
Longnecker et al. (1995) (16)/US	85	83
	[8]	**[5]**

[ ] percent associated with heavy drinkers, variously defined in different studies

There are more than 50 ecological, case-control, and cohort studies examining the association of alcohol and breast cancer (32). The majority, have reported consistent evidence for a positive association between breast cancer and alcohol intake (33). Case-control studies have provided the strongest evidence for an association between alcohol consumption and breast cancer. Rosenberg (17) gives a succinct review of the studies reported in the literature from 1982 through 1992. Studies were included if there were at least 200 prevalent cases with sufficient data on methodology and participation rates no lower than 60%. These studies primarily focused on recent drinking. A total of 18 studies were reviewed. One showed an inverse association and four reported odds ratios (ORs) close to the null (< 1.2), whereas eight of the 13 studies with positive associations reported ORs above the null, but $\leq$ 1.8. The remaining four positive studies reported at least one odds ratio above 1.8 and were hospital-based studies conducted in France (Odds Ratio (OR)=3.5 for > 17 drinks/week), and Italy (OR=2.2 for > 3 drinks/day; OR=2.2 for > 24.35 g/day; OR=2.4 for < 0.5 liters/day) (17). Population-based studies have reported lower estimates than hospital-based studies, ranging from 1.2 to 1.7, but have been hampered by lower participation rates of 60% to 80%. In these studies, stratification was not always made on the basis of menopausal status, an important effect modifier of the association between alcohol consumption and risk of breast cancer. However, associations were noted with alcohol intake prior to age 30. Estimates for dose-response

were inconsistent. Some studies showed an increase for those who consumed as little as one drink per day, while other studies reported an increased risk of breast cancer for those consuming only high levels of alcohol (17).

The eight cohort studies of breast cancer reviewed by Rosenberg ranged in follow-up time from 4 to 30 years, and were conducted in the U.S. (17) At least two suffered from high loss-to-follow-up rates. Results showed the following associations: null - 1; positive - 8. Overall relative risk estimates for studies ranged from 1.2 to 3.3. In the four studies with the majority of cases, the relative risk for breast cancer did not exceed 1.6, and was associated with an intake of at least 15+ g/day of alcohol (17).

The recent studies by Longnecker et al. (15, 16, 34) and Swanson et al. (14) built on the previous investigations, and many of their results are detailed below. The following provides a discussion of results for ever versus never lifetime alcohol consumption, dose-response, recent *vs.* past alcohol intake, beverage type, the association of alcohol and hormone levels in studies of human female subjects, as well as animal studies.

Ever *vs.* Never and Lifetime Alcohol Consumption

Longnecker et al.'s meta-analysis of 12 case-control studies reported an odds ratios for breast cancer of 1.4 (95% Confidence Interval (95%CI) 1.0-1.8) for consumption of 24 g/day of alcohol (2 drinks), and based on four cohort studies, a relative risk of 1.7 (95%CI 1.4-2.2) associated with consumption of 24 g/day of alcohol (34). Based on six of the case-control studies, the risk of breast cancer associated with 'ever' alcohol consumption was increased by only 10% (OR=1.1, 95%CI 1.0, 1.2). This attenuation is probably due to the fact that the majority of women were light to moderate drinkers and the inherent limitations present in the case-control design (34). In their case-control study, based on 15,825 subjects from four states, Longnecker et al. (16) ascertained pre- and postmenopausal incident breast cancer cases < 75 years of age who were diagnosed from 1988 through 1991, and reported to statewide cancer registries. A telephone questionnaire was used to assess alcohol intake of beer, wine, and liquor during five periods of life (16-19, 20-29, 30-39, 40-59, 60-74 years). Controls were drawn from two different sources and frequency-matched by age group. Average lifetime alcohol

consumption was based on the period from 16 years of age through the previous age interval. Lifetime average consumption for 13 g/day compared with lifelong abstainers was associated with a 31% increase in risk of breast cancer (95%CI 1.20-1.43), and a statistically significant trend across categories of alcohol consumption.

The recently reported case-control study by Swanson et al. (14), was based on 1,645 premenopausal incident breast cancer cases diagnosed during 1990-1992 in women 20 to 44 years of age, and frequency-matched to controls. The odds ratio for women defined as ever drinkers compared to nondrinkers was 1.1, (95%CI 1.0-1.3). A primary focus of this study was the effect of recent *vs.* usual alcohol intake by level of consumption, since previous studies had noted indirect evidence for the importance of recent alcohol intake. They evaluated alcohol usage patterns, exposure periods reflecting the teens, twenties, and thirties, beverage type, and stage of disease.

Dose-Response Relationship

The strongest evidence for a dose-response relationship of alcohol consumption and the risk of breast cancer comes from Longnecker et al.'s 1995 large, case-control study (16). Risk of breast cancer showed a monotonic increase by alcohol intake for all subjects combined with the exception of the highest category of alcohol intake (OR=1.75, 95%CI 1.16-2.64 for 46+ g/day alcohol). Results ranged from an odds ratio of 1.13 (95%CI 1.01-1.26) for 0-5 g/day alcohol, to 2.30 (95%CI 1.51-3.51) for 33-45 g/day alcohol (16). The risk estimate based on a continuous measure of the lifetime average number of grams of alcohol consumed daily was 1.31 (95%CI 1.20-1.43, P for trend <.0001) for 13 g/day (approximately 1 drink).

Swanson et al. (14), found an increased risk for breast cancer at a high dose (14+ drinks/wk) (OR=1.7, 95%CI 1.2-2.5), but no clear dose-response or gradient across categories of alcohol intake. Howe et al.'s study suggested a possible 'threshold' effect based on a pooled analysis of six case-control studies (35). A significant increase in risk was seen for women consuming 40 g/day or more of alcohol (OR=1.6 (95%CI 1.19-2.40), adjusted for total energy, fat, fiber, and vitamin C. The possibility of a threshold effect would require levels of alcohol intake to be high in order to detect an association.

In Longnecker et al.'s case-control study (16), risk was higher, although not statistically significant, for postmenopausal women compared to premenopausal women as noted below.

Average alcohol consumption g/day	**Premenopausal OR (95%CI)**	**Postmenopausal OR (95%CI)**
0	1.00	1.00
> 0-5	1.25 (0.97-1.61)	1.05 (0.94-1.17)
6-11	1.25 (0.93-1.67)	1.07 (0.92-1.24)
12-18	1.18 (0.83-1.67)	1.20 (1.00-1.44)
19-32	1.43 (0.96-2.13)	1.59 (1.28-1.98)
33-45	1.65 (0.88-3.10)	2.01 (1.37-2.95)
≥46	1.61 (0.90-2.86)	2.28 (1.51-3.44)
13 g/day	1.18 (1.03-1.36) P for trend = .02	1.27 (1.16-1.39) P for trend <.001

Longnecker et al. 1995:925(16)

Recent *vs.* Past Alcohol Consumption

Longnecker et al. (16) and Swanson et al.'s (14) investigations have shown a stronger association between 'recent' alcohol consumption and increased risk of breast cancer when stratified on time-period for alcohol consumption compared with "past" alcohol intake. In Longnecker et al.'s case-control study, 'recent' alcohol consumption was defined as intake in the previous age interval prior to the reference date, and 'past' alcohol consumption as intake prior to 30 years of age. Results indicated that 'recent' *vs.* 'past' alcohol consumption appeared to be more strongly associated with risk of breast cancer (OR=1.21 for 13 g/day alcohol, 95%CI 1.09-1.34 *vs.* OR=1.09 for 13 g/day alcohol, 95%CI 0.95-1.24). Swanson et al. reported a 70% increase in risk of breast cancer associated with 'recent' alcohol consumption (OR=1.70, 95%CI 1.2-2.5), although this was restricted to women consuming ≥ 14 drinks /week (14). Past alcohol consumption was based on the average intake for women during their teens, twenties, and thirties (14). Results by level of alcohol intake for the three age-period exposures indicated that risk increased 34% (95%CI 0.7, 2.6) in the teen years for consumption of ≥ 7 drinks per week, 29% (95%CI 0.9, 2.0) in the twenties for consumption of ≥ 14 drinks

per week, and 80% (95%CI 1.2, 2.6) in the thirties for consumption of ≥ 14 drinks per week. Stopping or reducing alcohol consumption may lower the risk of breast cancer regardless of recency of intake, even after mid-life (18).

Beverage Type

The pattern of risk by beverage type (wine, beer, hard liquor) has not always been consistent, and studies have varied as to which beverage, if any, carries the highest risk (36). This issue is a hard one to disentangle due to the mixture of beverages that tends to occur with alcohol consumption. Swanson et al.'s (14) study reported the strongest risk for beer consumption (OR=2.6, 95%CI=1.4-4.8) compared to wine and liquor intake; whereas Longnecker et al.'s (16) study showed an increased risk for both beer (OR=1.25, 95%CI=1.13-1.39) and liquor (OR=1.18, 95%CI=1.07-1.31). Mutual adjustment for beverage type in the study by van den Brandt et al. (33) suggested that the association was present for wine (OR=1.50, 95%CI 0.63-3.57), and liquor (OR=1.67, 95%CI 0.82-3.39), but not for beer consumption (OR=0.95, 95%CI 0.61-1.48). However, associations reported for one beverage *vs.* another may merely reflect the dominant beverage consumed by the heaviest drinkers. Although some studies have shown a difference in risk by beverage type, risk has not been consistently associated with one type, implying that risk is associated with alcohol intake in general, and not with any other specific component.

Association of Alcohol and Hormone Levels

There is no definitive evidence for a causal mechanism associating alcohol consumption with breast cancer risk. However, a small clinical trial has proposed a possible mechanism for the positive association between alcohol consumption and breast cancer, with the detection of a statistically significant increase in plasma and urinary hormones. A group of 34 premenopausal women, aged 20-40 years, was enrolled in a controlled-diet study for six consecutive months. Subjects served as their own controls to reduce interindividual variation. Following exposure to 30 g/day of ethanol for three menstrual cycles, they abstained from alcohol for the remaining three cycles. Results showed elevated serum levels of total and bioavailable estrogen (37). An increase in

plasma estradiol levels has been shown to also increase three-fold in postmenopausal women following a single dose of 0.7 g/kilogram (kg) alcohol (38).

The link of alcohol with estrogen level provides a rational mechanism between alcohol intake and breast cancer, implying an effect on estrogen production and metabolism. Estrogen and progesterone are required for the cyclic proliferation of mammary ductal cells during the menstrual cycle and for lobuloalveolar growth during pregnancy. Hormonal level is hypothesized to be important in the etiology of breast cancer by increasing breast epithelial cell division during relevant developmental periods, and enhancing the possibility of carcinogenesis (39). Studies in the 1970s established increased plasma estrogen and estradiol levels in postmenopausal women with breast cancer (40), supporting the hypothesis that breast neoplasia is the result of excessive hormonal stimulation.

Results based on experimental animal models of alcohol exposure and breast cancer are inconsistent (41-43). These studies are difficult to conduct, because there are few good animal models of spontaneous breast cancer. Most studies are conducted using rodents; dogs, although they develop natural spontaneous breast tumors, are considered too expensive for most studies (41). Most studies report no association between alcohol and mammary carcinogenesis (42). McDermott et al. (42) conducted an experiment in which female Sprague-Dawley rats given an established carcinogen were randomly assigned to dietary ethanol (4.4g/kg/day) or placebo. The incidence of tumors was significantly lower in the ethanol than control group ($p < 0.001$), and there was no statistically significant difference between groups in mean number of tumors, tumor growth rate, or time of appearance of first tumor. Endocrine levels were not measured for the two groups. Positive results have shown that ethanol consumption > 20% of calories decreased serum progesterone and mammary gland maturation and differentiation resulting in an increase in the density of carcinogen sensitive histological structures (44, 45). These changes might increase susceptibility to breast cancer carcinogens, but would not necessarily cause cancer. It has been suggested that progesterone when co-occurring with estrogen may further increase mitotic activity in breast epithelium (46).

Reasons cited for the inconsistent or negative results from animal studies include mode of ethanol administration (gavage, drinking water, liquid diet), and amount of ethanol administered which has usually been 20% or more of total calories with no evaluation of lower doses (43). These factors are thought to have an effect on the rate of ethanol absorption, level and duration of ethanol, and blood-level metabolites, all of which might subsequently affect metabolism (43). Ethanol administered as part of a natural product diet *vs.* a liquid diet may also result in tumor response variation (43).

In summary, a majority of both case-control and cohort studies indicate an increased prevalence of alcohol intake in cases, an increased incidence of breast cancer in those drinking > 14 g/day, an increased risk associated with dose, as well as risk differential associated with timing of exposure (recent *vs.* past alcohol intake). In general, risk appears to be associated with alcohol consumption regardless of beverage type, suggesting that ethanol is the actual risk factor. Although the weight of experimental animal studies does not tend to support the alcohol-breast cancer risk hypothesis, small human clinical studies have suggested that alcohol exerts an effect on breast cancer risk by increasing estrogen levels. These changes might increase susceptibility to breast cancer carcinogens by acting as promoters. Although the scanty results from animal experiments have been inconsistent for breast tumorigenesis, alcohol is still an established carcinogen for other cancer sites and its effect on serum hormone levels has been identified (18). By analogy, the pattern for the association between breast cancer and alcohol, as well as other known or considered risk factors, does not appear dissimilar. Certainly, the risk associated with several of the reproductive factors (early age at menarche, late age at menopause, absence or short duration of breastfeeding) is within the 1.5 to 2.0 range, which covers the estimate generally reported for alcohol and breast cancer (47). Although not all studies were conducted with an '*a priori*' hypothesis, and the effect is modest, there is a consistency in the trend and magnitude of the well-designed large studies (48).

Hormone Receptor Status of Breast Tumors

Hormone receptor status has received attention as a means of identifying subtypes of breast cancer that are not only related to prognosis and survival, but possibly to

separate risk factors for breast cancer (19, 20). Estrogen receptor protein binds and transfers estrogen to the nucleus of a cell, and is found in about 60% of breast cancers (49). The number of estrogen receptors in breast cancer cells is associated with cell differentiation, with tumor response to antiestrogen or tamoxifen therapy, and to oophorectomy (50). Receptor-positive tumors are reported to occur more frequently among postmenopausal women than among premenopausal women (49). Patients with both ER+/PR+ status are characterized by the highest response rates (approximately 70%) to endocrine therapy, whereas those with ER-/PR- tumors (approximately 10%) show the poorest response, and those with discordant status (30-40%) show an intermediate response (51 249, 52)

Several studies have demonstrated an association of alcohol consumption with hormone receptor status, although analyses and results have varied by use of separate subtypes, ER or PR status, (21), or the joint combination of ER/PR status (22, 23). Risk factors for breast cancer, including family history of breast cancer (53), body mass index (BMI) (54), dietary fat (24, 55), parity, age at first birth, age at menarche, and body fat distribution (23) have shown different patterns by hormone receptor status. These results may suggest different etiologies associated with disease heterogeneity or separate hormone receptor subtypes. Based on data from a case-control study conducted in New York (1982-1984) of 1,152 women, aged 20-79 years of age, Nasca et al. reported an odds ratio of 1.18 (95%CI 0.88-1.57) for <1.5 g/day alcohol with an increase to 1.35 (95%CI 0.99-1.85) for ≥15.0 g/day alcohol associated with ER+ breast tumors (21). Breast cancer cases with ER+ status were more likely to be ≥ 65 years (64%) compared to ER- cases (54%), to have reported the cessation of menstruation (77% *vs.* 68%), and to have a greater duration (14+ years) of cigarette smoking (37% *vs.* 30%), following adjustment for covariates.

Data from the cohort, 'Iowa Women's Health Study', based on 610 (65%) women with a joint ER/PR status out of 939 women identified with incident breast cancer and aged 55-69 years, showed an association between PR+ status and risk factors which measure endogenous hormone exposure (23). However, alcohol use within the last year was found to increase the risk for ER-/PR- breast tumors in both stratified (RR=1.55

(95%CI 1.00-2.41), and polychotomous logistic regression analyses (RR=1.37 (95%CI 0.86-2.18). Gapstur et al. (22) extended analyses of the 'Iowa Women's Health Study' to evaluate the risk of breast cancer hormone receptor status and the presence of interaction between alcohol consumption (0, < 4.0, ≥ 4.0 g/day) with three other risk factors. ER-/PR+ was excluded due to small sample size. Relative risks by hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR-) for those on estrogen replacement therapy were reported to be 1.8 (95%CI 1.3-2.5), 1.3 (95%CI 0.6-2.5), and 2.6 (95%CI 1.4-4.9) respectively, at the highest alcohol intake of ≥ 4.0 g/day. Results for family history were 1.7 (95%CI 1.2-2.5), 0.8 (95%CI 0.3-2.3), and 3.1 (95%CI 1.6-6.2) for women with any level of alcohol intake, and results for the highest quintile of BMI > 30.70 were 0.9 (95%CI 0.5-1.9), 1.8 (95%CI 0.7-4.7), and 2.0 (95%CI 0.7-5.6) for 'drinkers' (22)

In contrast to these results, the initial analyses of the association between alcohol consumption and breast cancer for the 'Iowa Women's Health Study' showed only an age-adjusted relative risk of 1.28 (95%CI 0.93-1.76). This risk increased (RR = 1.46, 95%CI 1.04-2.04; P for trend=0.04, for the highest alcohol intake of 15+ g/day) with adjustment for covariates (BMI, age at first livebirth, age at menarche, and family history of breast cancer) (56). Significant multiplicative interaction was detected between alcohol intake and noncontraceptive estrogen use for the two highest levels of alcohol intake (RR=1.88, 95%CI 1.30-2.72 for 5.0-14.9 g/day; RR=1.83, 95%CI 1.18-2.85 for 15+ g/day), whereas there was no association between alcohol and breast cancer detected among never-users of estrogen (56).

The association of ethnicity with hormone receptor status was examined for 13,239 breast cancer cases in the 'Patient Care Evaluation Study of Breast Cancer', ascertained during 1990 (26). The status group ER+/PR+ was used as the referent group in the polychotomous logistic regression analysis which did not show a significant difference for ER/PR status for Hispanic *vs.* non-Hispanic white women: ER+PR-, OR=0.88 (95%CI 0.65, 1.21); ER-PR+, OR=1.20 (95%.CI 0.83, 1.75; and ER-PR-, OR=0.95 (95%CI 0.74, 1.23). However, this may be due to the lack of a true nondiseased control group.

Studies of Hispanic Ethnicity and Breast Cancer Risk

Studies have shown that incidence and mortality rates for other chronic diseases such as diabetes and heart disease also show a different pattern for Hispanics compared with non-Hispanic whites in New Mexico (57). The majority (75%) of Hispanics residing in New Mexico are primarily lifelong residents, compared to only 15% of non-Hispanic white women. Additionally, for many, their families have lived here for several generations, and are composed of descendants of Spanish colonists of the 16th, 17th, and 18th centuries who intermarried with Pueblo Indians and recent Mexican immigrants. Thus, they are not strictly comparable to other Hispanic groups such as Mexican-Americans who are recent immigrants to the United States. However, the Hispanic population in the U.S. is characterized by a diversity across a spectrum of factors, including background nationality, ethnicity, socioeconomic status, social class, culture, and religion (7).

As noted previously, there are few published studies comparing Hispanic women with other ethnic groups for breast cancer. Two studies conducted in Texas reported a lower incidence of familial breast cancer among Hispanic women compared to Blacks and non-Hispanic whites (8), and the suggestion of an increased risk of mortality due to breast cancer with increased age at first child-birth (4). Hispanic women, over the period 1980 to 1992, were reported to have more late stage breast cancer than non-Hispanic white women (37% *vs.* 28%), and to be less than 50 years old at age of diagnosis (44% *vs.* 28%) (58). In contrast, based on SEER data, Hispanic women were reported to present at an earlier stage of diagnosis for the time-period 1983-1992 compared to 1973-1982. However, although detection now occurs more frequently at the local stage, survival has not improved (59). In an analysis of the 148 Hispanic cases and 167 controls (43% based on New Mexico Hispanics) drawn from 'The Cancer and Steroid Hormone Study (CASH)', a statistically significant increased risk for breast cancer was found for women who reported having a mother or sister with a history of breast cancer (OR=1.89) (9). Although not statistically significant, the expected pattern for number of full-term pregnancies, age at first full-term birth, and benign breast disease were found, but not for early age at menarche.

Latino ethnicity was found to be a significant predictor of dietary and alcohol intake after adjustment for relevant covariates in a study of California Latino dietary practices (11). Latinos compared to non-Latino whites were less likely to have had liquor in the past month (OR=0.6). Less acculturated (greater use of Spanish language) Latinos compared with highly acculturated (greater use of English) Latinos reported less alcohol consumption in the past month (OR=0.7). Post-menopausal Hispanic women in New Mexico, compared to non-Hispanic whites, are reported to have a similar intake of beer, but less intake for wine and liquor (60) and overall, alcohol consumption is lower.

In a study of 6,678 breast tumor specimens, Elledge et al. reported that Hispanic women had worse overall 5-year survival compared to non-Hispanic white women (65% *vs.* 75%), and differed for tumor biologic factors (61). Significant differences, based on the Hispanic *vs.* non-Hispanic white comparison, were present for age (61% *vs.* 76%), tumor size (32% *vs.* 45%), and nodal status (30% *vs.* 21%). Age was found to modify the association between ethnicity and hormone receptor status. Hispanic women were intermediate to non-Hispanic whites and Blacks for ER+ status tumors for ages 35 to 50 years, (P for difference < 0.12), and for 50 years or greater (P for difference <.002). This was also true for PR+ status for women 50 years of age or older (P for difference < 0.006) (61).

BODY

MATERIALS and METHODS

The data for this study were drawn from the 'New Mexico Women's Health Study' (NMWHS), a statewide population-based case-control study of breast cancer in Hispanic and non-Hispanic white women. Incident cases diagnosed with an invasive or *in situ* breast carcinoma during the period January 1, 1992 through December 31, 1994, who were aged 30 through 74 years of age and residents of New Mexico at diagnosis, were eligible for the study.

Selection Of Case Subjects

All eligible Hispanic cases were included. Hispanic ethnicity was based on Spanish surname identified by means of a computer program based on the 1980 Census Bureau list of Spanish surnames, and a computer program (GUESS) that evaluates beginnings, endings and specific letter combinations in a last name (62). The overall expected number of breast cancer cases for the study period was approximately three times higher for non-Hispanic cases compared with Hispanics. A random sample of approximately 33% of non-Hispanic white cases based on age group (30-39, 40-64, 65-74 years) and geographic region, defined by seven state health planning districts, was identified for inclusion. The sampling fraction for non-Hispanic whites in each of these 21 strata was chosen to give a distribution similar to the age and geographic distribution of Hispanic cases ascertained by the NMTR in the three-year period 1988 through 1990. There was a total of 491 eligible Hispanic breast cancer cases. Random selection of non-Hispanic whites resulted in 493 cases. Of the eligible cases, 332 Hispanic (67.6%) and 380 non-Hispanic white women (77.1%) completed interviews. These response rates are lower than for controls (see below), and for the in-person interview study of alcohol consumption reported by Swanson (86%) (14), and the telephone-based interview reported by Longnecker (80%) (16). However, state-specific response rates in Longnecker et al.'s study ranged from 74% for Maine to 86% in New Hampshire among four states. These studies were based primarily on non-Hispanic white subjects.

Selection Of Control Subjects

Controls were frequency-matched on the basis of Hispanic and non-Hispanic white ethnicity, three age groups (30-39, 40-64, 65-74), and seven health planning districts. Controls were ascertained through a modified approach to the Waksberg random digit dialing method (63). Data from the NMTR collected over the past 26 years were used to build a pool of prefixes known to contain residential numbers for control selection. This pool was based on those prefixes which had contributed at least one breast cancer case to the NMTR database. This restricted pool of prefixes was used to increase the likelihood of generating a larger pool of 'working' residential phone numbers; a real concern due to the sparsely populated counties of New Mexico. Additionally, a random sample of phone numbers linked to gender, health planning district, ethnicity, and age-group were used to efficiently locate and recruit a sufficient number of older, rural Hispanic controls due to the difficulty in ascertaining this subset of women.

A total of 8,147 working telephone numbers were contacted; of these, 4,459 were residential numbers. There were a total of 1,039 eligible controls ascertained from 3,400 respondents who completed the telephone screening interview; 511 Hispanic and 528 non-Hispanic white women. Of these, 388 (75.9%) Hispanic, and 456 (86.4%) non-Hispanic white women completed interviews. Overall response rates for controls stratified by ethnicity could not be calculated because ethnicity of non-respondents was unknown. However, the response rate for Hispanic control subjects is comparable to that for Swanson et al.'s study (78.7%) (14), and the response for non-Hispanic white controls is similar to the rate reported by Longnecker et al. (84%) which ranged from 79% in Massachusetts to 90% in Wisconsin (16).

Data Collection

The University of New Mexico's Human Research and Review Committee approved the NMWHS project. Physician consent was obtained for all cases and a written informed consent was signed at the onset of the interview. Interviews were conducted in-person at a subject's home or an agreed upon location and averaged 1½ hours.

All questionnaires were translated into Spanish, and interviews were conducted in Spanish or English by bilingual interviewers according to the participant's preference. The RFQ included questions on demographic characteristics, education, income, ethnic identification and acculturation factors, and primary breast cancer risk factors related to reproductive and menstrual history, use of oral contraceptives and exogenous hormones, family history of breast disease, personal history of breast disease, history of radiation, weight, height, physical activity in the prior year, as well as cigarette smoking, and history of alcohol consumption. To aid respondent recall, interviewers used a calendar that recorded their major life events. Ethnicity was based on the subject's self-report at the time of interview. Subjects who reported Hispanic or non-Hispanic white ethnicity are included in the analyses. Interviewers were not informed as to case-control status, and the alcohol and dietary data for the FFQ was collected at the beginning of the interview.

Recent dietary intake, including alcohol consumption based on intake of wine, beer, and hard liquor, was collected using a semiquantative food frequency questionnaire. The FFQ was designed by staff of the Human Nutrition Center at the University of Texas, Houston School of Public Health, and was a modified version of one used in a Texas Hispanic population (64). Modifications were made by Dr. R. Sue McPherson to add foods to the FFQ that were important sources of nutrients among New Mexico women. Following an analysis of food intake recalls of 100 women, based on local food sources of energy, macronutrients and vitamins were added to the FFQ resulting in a 140 item questionnaire. Standard protocols for the development of the FFQ were used (65, 66). Emphasis was placed on adding specific foods, rather than grouped foods, because recall is considered to be better for specific items (67, 68). Frequency of use information included consumption on a per month, week, or day basis, and was averaged over a 28-day month for an estimated daily intake. Two-dimensional food models were used to aid in the determination of portion size which included data on number of servings, the type of food model, and thickness of food as appropriate. Frequency of consumption and portion size data were entered into the 'Food Frequency Data Entry and Analysis Program' which contained the gram weight and nutrient data to calculate nutrient estimates per food

per day (69). In an effort to avoid the potential impact of disease or treatment, all subjects were asked to recall 'usual' food intake for a four-week period six months prior to the interview. If a subject reported that their diet was not 'usual' during this time, due to any reason, they were asked to recall the months prior to any major impact on 'usual' food intake.

The following sections describe the statistical methods applied and results of analyses conducted as of the date of this report.

STATISTICAL METHODS

Dependent Variable

For the results presented in this report, breast cancer was defined as all diagnosed incident invasive or *in situ* breast carcinomas. Hormone receptor assays were conducted in laboratories associated with the hospitals where cases were diagnosed. Estrogen and progesterone receptor status are separately coded by the SEER Program as: none done (0); positive (1); negative (2); borderline or undetermined (3); ordered, but results not in chart (8); and unknown (9). Breast cancers were categorized by the joint classification of ER/PR status (ER+PR+, ER+PR-, ER-PR+, ER-PR-, unknown). If either ER or PR status was unknown, the joint status was considered 'unknown'.

Alcohol Exposure Variables

In the present report, several variables were created to express alcohol consumption in terms of both recent intake and past history. 'Recent' alcohol intake, as measured by the FFQ, was expressed in grams per day, and average daily alcohol consumption was based on the summation of the three beverage types. The ethanol content for each type of beverage was based on the standard amount reported in the USDA Nutrient Database for Individual Intake Surveys, Release 7.0: 12.6 g/alcohol for one serving of beer; 12.6 g/alcohol for one 3 ½ -ounce glass of wine; and 21.2 g/alcohol for one hard liquor drink (70). Alcohol abstinence (nondrinkers) was defined as an intake of 0 grams per day.

Questions on alcohol intake in the RFQ included ever *vs.* never use, age at first use, and age at cessation. History of 'past' use included frequency of drinking, and

number of drinks per week by beverage type at age 25, 35 and 50 years. Frequency of drinking included: 4 or more times per day; 2-3 times per day; once per day; 2-3 times per week; once per week; once per month; 2-3 times per month; 2-3 times per year; and never. The ethanol content for each type of beverage was based on the USDA standard amount as described above for "recent" intake from the FFQ. Beverage type was not included in analyses because there has been no consistent evidence to suggest its importance independent of ethanol content.

Confounding Variables

The covariates considered in the present analyses were selected based on several previous studies, and included: education; age at menarche; age at first full-term pregnancy lasting six or more months regardless of pregnancy outcome; parity based on pregnancies of six or more months resulting in either a single birth, multiple birth, or a stillbirth; cumulative months of lactation; menopausal status (premenopausal, postmenopausal, surgical unknown); benign breast disease; family history; oral contraceptive use; family history of breast cancer for mother, sister, or daughter; current BMI (weight(kg)/height(m)^2) calculated from the self-reported height and weight; BMI at age 18 calculated from height and weight at age 18; smoking for six months or more; physical activity as metabolic equivalents (METS)/week for vigorous activity over the previous year; total caloric intake in kilocalories (kcals); and total fat intake (g) (13, 14, 16, 31, 34, 36, 56, 71-74).

Estrogen replacement therapy was not included as a covariate, because it was used together with self-report of menstrual history, and history of hysterectomy with or without oophorectomy, to define menopausal status. Subjects who could not be assigned menopausal status based on these criteria were categorized as pre- or post-menopausal when age was below the 10th percentile (43 years) and above the 90th percentile (54 years), respectively.

Data Analysis

In preliminary analyses, variables were evaluated for missing data, outliers, and small samples for categories of exposure using descriptive summaries. Analyses were based on all subjects combined, and stratified by ethnicity.

Conditional, fixed-effects, logistic regression was used to determine univariate odds ratios and the corresponding 95 percent confidence intervals for the alcohol exposure variables and covariates (75). Logistic regression analyses based on all subjects were conditioned on the three matching factors (3 age-groups, seven health planning districts, Hispanic and non-Hispanic white ethnicity). Analyses stratified by ethnicity were conditioned on age and health planning district. Age was included additionally in all models to adjust for residual age differences between cases and controls. Age was defined as age at diagnosis in cases and age at interview in controls.

Several factors reduced sample sizes for some analyses. There were five non-Hispanic white controls in age group 30-39, planning districts 4 and 5, and four Hispanic controls in age group 30-39, planning district 5, and age group 65-74, planning district 1, who were dropped from the conditional logistic regression analyses because there were no cases in those particular strata. As a result, the total sample size for the logistic regression analyses was 1,547 (716 Hispanic, 831 non-Hispanic white).

Total energy intake based on the FFQ was restricted to 500-6,000 kcals. There were no subjects who reported an intake < 500 kcals/day. The majority of those with energy intake > 6000 kcals/day had very low daily alcohol intake (<10.0 g) with the exception of one subject who reported an intake of 68.07 g. A total of 16 subjects with an energy intake $\geq$ 6,000 kcals/day were excluded from analyses of recent alcohol intake based on the food frequency questionnaire (FFQ) data; in addition, there were 7 subjects excluded due to incomplete or no FFQ data. An evaluation of the 'past' alcohol exposure variables included the recoding for 30 subjects from drinkers to non-drinkers, because their first age and stop age for alcohol consumption was the same. These subjects reported no past use of alcohol for any of the age points; 73% of this group reported a first age of 25 years or less, and only four reported an age at first use to be 35 or greater.

Relevant covariates were evaluated in combined and ethnic-specific analyses. Most previous studies have categorized these variables. Category boundaries for variables that were not dichotomous were defined either on the basis of commonly accepted cutpoints, or on the basis of the quantile distributions among combined controls. Categorized variables were evaluated to determine whether final groupings were too broad to detect dose-response changes or too narrow to provide stable estimates (76). All data analyses were performed using SAS (77) and STATA (78). Conditional logistic regression analyses were made using STATA procedures (78).

RESULTS - PRELIMINARY

Descriptive Statistics

The majority of cases were diagnosed with intraductal carcinoma (65.5%), followed by lobular carcinoma (8.58%), comedocarcinoma (5.91%), and infiltrating ductal and lobular carcinoma (4.50%). Although frequency of stage at diagnosis followed the same trend for both ethnic groups, regional disease at diagnosis was somewhat higher for Hispanic women (32.83%) compared with non-Hispanic white women (24.47%). Local disease and *insitu* stage was likewise lower for Hispanic women (49.10% and 14.46%) compared with non-Hispanic white women (53.95% and 18.68%).

The mean age of cases at diagnosis was 53.66 years (Standard deviation, [SD]=11.04) compared with 52.44 years (SD=11.72) for controls at time of interview (Table 1). Only a small percentage of interviews were conducted in Spanish (3%), and 93% were home-interviews. The majority of Hispanic subjects were lifelong New Mexico residents (75%), compared with non-Hispanic whites (15%). Hispanic and non-Hispanic white women differed primarily for age at first full-term birth, age at menopause, usual BMI, total energy and total fat intake, vigorous physical activity, as well as for all alcohol-related variables. Case-control differences were related primarily to age at first alcohol intake, total fat intake, and vigorous physical activity. Most noticeable, was that Hispanic cases reported fewer drinks per week at age 25 than controls, similar intake at age 35, but increased intake at age 50.

Table 2 describes the distributions of demographic variables by ethnicity and case-control status. Hispanic women, 30 to 39 years of age, accounted for a greater percentage of the cases than non-Hispanic white women (12.7% *vs.* 8.7%), and therefore more premenopausal cases. Socioeconomic status, measured by education and income, differed across the two ethnic groups as well as by case-control status. Hispanic women were generally younger at their first full-term birth and had a higher parity than non-Hispanic white women. Hispanic women tended to report a higher BMI at age 18 years, and markedly higher usual BMI: 40% of Hispanic cases had BMIs $\geq$ 25.68 kg/m^2, compared to 32% for Hispanic controls, and approximately 17% to 18% for non-Hispanic white women. In general, cases reported lower energy and total fat intake than controls, with Hispanic women reporting higher levels than non-Hispanic white women. A family history of breast cancer among first degree relatives was increased for cases. Controls reported high levels of vigorous physical activity more frequently than cases, and Hispanic women (36%) reported no physical activity more frequently than non-Hispanic whites (24%).

Table 3 shows distributions for alcohol exposure variables by ethnicity and case-control status. Alcohol consumption was a common exposure among subjects (83%) with cases (81%) and Hispanic women (77%) reporting a slightly lower frequency. Status of drinking showed that cases reported being 'current' drinkers about 10% less frequently than controls, with controls reporting an earlier age at first use. In general, alcohol intake was reported by Hispanics, and by cases, to be lower than non-Hispanic whites and controls. This trend was also true for frequency of drinking, overall alcohol intake measured in grams, and number of drinks at ages 25 and 35 y. Cases, however, reported consumption of alcohol slightly more frequently at 50 y than controls, although the overall trend for consumption across the three age points decreased. Consumption of alcohol on a daily or weekly level was very low at all three ages, especially in Hispanic women who reported daily and weekly intakes about one-half as often as non-Hispanic whites. Non-Hispanic white women reported drinking 6 or more drinks per week about twice as often as Hispanic women at ages 25 and 35 y, and were about 6 times more likely to do so at age 50 y. Alcohol intake based on the FFQ daily gram estimate showed

that only 47% of all subjects reported alcohol consumption in the four-week period six months prior to the interview. Reported alcohol intake was very low with only a small percentage reporting even moderate levels. Again, the overall level of consumption reported on the FFQ was higher in non-Hispanic white compared to Hispanic women.

In preliminary analyses, the percentage for 'no hormone receptor status ordered', was comparable for the two ethnic groups, at approximately 15% (not shown in a table). The number 'unknown' was lower for Hispanic cases (9.3%) compared with non-Hispanic white women (12.1%), and the ES-/PR- status was higher for Hispanic cases (23.8%) than for non-Hispanic white cases (17.1%). The remaining hormone receptor status groups were similar for the two ethnic groups: approximately 40.0% for ES+/PR+, about 10.8% for ES+/PR-, and; 2.8% for ES-/PR+ which may need to be dropped from analysis. The prevalence rates for ER+ (51.48%), ER- (27.2%), PR+ (43.32%), PR- (31.50%), and the number unknown (approximately 25% for both ER and PR status), compare favorable with those reported by Gapstur et al. (22), in which the prevalence of ER+, ER-, and ER missing was 59%, 11%, and 30%, and the prevalence for PR+, PR-, and PR missing was 46%, 19%, and 35%. In Nasca et al.'s study on ER receptor status and alcohol consumption, 25% of subjects had missing data (21).

Co-morbid conditions were similar in distribution by both case-control status and ethnicity with the exception of diabetes, gallbladder disease, and rheumatoid arthritis, which were higher in Hispanic women, at 12%, 19%, and 11%, compared with non-Hispanic white women at 4%, 13%, and 6%, respectively (Table 4).

Univariate Results

Table 5 shows age-adjusted odds ratios for selected covariates. The majority of risk factors followed the expected risk pattern reported in previous studies (47). The risk of breast cancer for Hispanics was increased for women of low SES, but there was no trend for non-Hispanic whites. Ever-married was associated with a weak protective effect (OR=0.73 95%CI) 0.46-1.14) for all subjects. Results for menopausal status did not show the same trend in both ethnic groups, and the risk was increased most for the 'surgical unknown' group that could not be categorized on the basis of age, as described previously. Risk was increased in non-Hispanic white nulliparous women and those with

parity ≤ 2, but not in Hispanic women. Risk was increased in those with age at first birth > 27 y (OR=1.36 95%CI 0.95-1.96). This association was stronger in non-Hispanic whites than Hispanics. Duration of lactation greater than 12 months showed a protective effect in both ethnic groups and for all women (OR=0.68 95%CI 0.44-1.06) relative to parous women who had never breast-fed. Benign breast disease increased risk among both ethnic groups (overall OR=1.52 95%CI 1.15-2.01), as did family history of breast cancer (overall OR=1.36 95%CI 1.00-1.85). Usual body mass index was associated with an increased risk of breast cancer for Hispanic women only at all three levels with an odds ratio of 2.38 (95%CI 1.46-3.87) for women with a BMI >25.68. There was no discernible trend for BMI at age 18 y. Results for smoking did not show an increased risk (overall OR=0.84 95%CI 0.68-1.03). Vigorous physical activity was protective, showing a trend in effect with increasing levels of vigorous activity (overall OR for 0 to12.5 METS=0.59 95%CI 0.45-0.76 *vs.* overall OR for 12.6 to 35.0 METS=0.59 95%CI 0.45-0.76). The results for energy and total fat did not show any particular trend, although these results are not based on any transformed measure to account for skewed distribution nor are they energy-adjusted. These variables along with 'recent' alcohol intake as measured on the FFQ will be further evaluated in the future analyses.

Although both variables, education and income, were evaluated at the univariate level, education was selected for further evaluation as a confounder because the two variables were correlated (Spearman's rank correlation coefficient, r=0.46), and income compared with education was missing for more subjects (59 *vs.* 6). The measures of body mass index, 'usual' and past index at 18 years of age also were highly correlated (r=0.51). 'Usual' BMI was selected to include in analyses because it is more likely to be associated with both recent and past alcohol intake than BMI at 18.

Age-adjusted odds ratios for alcohol exposure variables are shown in Table 6. Alcohol consumption (ever *vs.* never), showed a modest protective effect, although not statistically significant (OR=0.80 95%CI 0.60-1.06). This protective effect was significant, however, for all women who were current drinkers (OR=0.70 95%CI 0.52-0.94), in contrast with former drinkers who showed a slightly increased risk. The association in former drinkers was further found to be due primarily to cases (n=44) who

reported that they stopped drinking at the time of diagnosis (overall OR=8.98 95%CI 3.41-23.66). Risk was also increased, although to a much lesser extent, in those who stopped drinking within one to four years prior to diagnosis in both ethnic groups. In general, women who stopped drinking five or more years prior to diagnosis showed a decreased risk. Current drinkers also showed a significant protective effect for all women combined (overall OR=0.72 95%CI 0.54-0.97).

Because of the strong effect due to a small group of women, accounting for only 6% of all cases, but 25% of cases who were former drinkers, estimates for several alcohol exposure variables were recalculated. Separating this group out resulted in estimates for former drinkers (OR=0.78 95%CI 0.55-1.11) that were closer to those for current drinkers (OR=0.71 95%CI 0.53-0.95). There was little change in the estimates for age at first use of alcohol.

A trend for a protective effect was seen with an early age at first use (OR=0.56 for <=16; OR=0.67 for 17 to 18). Results for duration of drinking suggested the presence of a statistically significant protective effect for 40 or more years for both ethnic groups, as well as for all women (overall OR=0.63 95%CI 0.43-0.92). Past alcohol intake at age 25, 35, and 50 also showed a protective effect. Results for frequency of drinking, gram intake, and number of drinks at ages 25, 35, and 50 are more difficult to interpret, however, because so few women drank more than a small to moderate amount of alcohol.

Recent alcohol intake as reported on the FFQ showed an increased risk for non-Hispanic white women consuming more than one drink of alcohol (> 21.20 g) on a daily basis (OR=1.31 95%CI 0.78-2.21), although this was not statistically significant. It was difficult to evaluate any dose-related trend as so few women reported more than light drinking. Additionally, these results are preliminary as these were absolute values for alcohol intake adjusted only for age. Final analyses will include total energy and energy-adjusted total fat as covariates.

Multivariate Results

Table 7 shows results for multivariate models adjusting for education, age at menarche, menopausal status, age at first full-term birth, parity, breastfeeding, benign breast disease, years of oral contraceptive use, usual BMI, smoking, family history of

breast cancer, and physical activity, in addition to age, for selected alcohol exposure variables. Overall, the effect of adjustment for these additional covariates was to increase odds ratios, particularly in Hispanics. For example, adjustment in the multivariate model increased the odds ratio for current drinkers in Hispanics from 0.69 (Table 6) to 0.88 (Table 7). In contrast, the odds ratio for current drinkers in non-Hispanic whites decreased somewhat in the multivariate model compared to the age-adjusted univariate model (OR=0.61 vs. 0.67). The odds ratio for duration of drinking >40 y increased in Hispanics, but not in non-Hispanic whites, and the overall estimate was no longer significantly protective (OR - 0.75 95%CI 0.49-1.13, Table 7) compared with estimate shown in Table 6.

CONCLUSIONS

A lower response rate was observed in the present study for Hispanics compared with non-Hispanic whites. Although this raises the possibility of selection bias, it cannot be determined to what extent this may affect results. It should be emphasized that there are few studies of breast cancer in Hispanic women and the overall response rates in the present study, especially for non-Hispanic whites, were similar to other larger case-control studies.

Based on the initial analyses presented above, a few general, but preliminary, statements can be made about the association of alcohol consumption with risk of breast cancer in this study. Overall, the preliminary univariate results based only on age adjustment indicate, in contrast to recent studies, either no effect of alcohol intake, or even a slight protective effect for light to moderate alcohol intake. An effect of heavy alcohol intake is difficult to evaluate because there were so few heavy drinkers in the study. The relatively low level of alcohol consumption observed in the present study, especially in Hispanic women, agrees with data reported from other studies conducted in New Mexico (60). It is not possible to determine at this time whether the apparent protective effect observed is indirect and due to confounding with other health-related behaviors, or whether there is a direct biological effect of light to moderate alcohol intake on breast cancer induction or promotion. The preliminary results from the multivariate analyses conducted to date generally indicate that point estimates of odds ratios for many alcohol exposure variables tend to move towards the null value (1.00) when adjusted for multiple, potentially confounding variables, such as better education, more vigorous physical activity, and other factors. This appears to support the hypothesis that the "protective" effect of light to moderate alcohol intake may be indirect and due to the association of this drinking pattern with other healthy behaviors.

A second observation from the preliminary analyses is that there is a subgroup of subjects, mostly cases, who stopped drinking at the time of diagnosis, and therefore appear to increase risk estimates for 'former' drinkers. It is possible that this subgroup of women stopped drinking due to some information they had or received on a possible association of breast cancer risk with alcohol consumption, and therefore introduce

information bias. They also affected estimates of 'recent' drinking because they provided no FFQ alcohol data. It remains to be determined if they additionally affect estimates of 'past' drinking due to systematic underreporting of alcohol intake at previous ages.

A third observation is that the pattern of risk factors for breast cancer, as well as the specific association of alcohol consumption, may differ somewhat between Hispanic and non-Hispanic white women. More work remains in better defining ethnic differences in risk factor patterns. Different prevalences of comorbidity, particularly non-insulin dependent diabetes, gall-bladder disease, and rheumatoid arthritis were observed in Hispanic compared to non-Hispanic white women in the present study, which agrees with multiple previous studies in New Mexico (57). It is not clear at present if these ethnic differences in co-morbidity have any influence on breast cancer risk or on patterns of risk factors.

The final report will address relevant limitations of case-control studies, such as selection, confounding, and information biases, in greater detail. In compliance with the original 'Statement of Work' (see Appendix A-2), the following section reviews the completed tasks and summarizes plans for the final grant year.

Statement Of Work

Year 01 - Completed Tasks: During the first performance period (September 1, 1996 - August 31, 1997) of the predoctoral fellowship, an advisory committee was formed in the Fall, 1996, composed of: Dr. John F. Annegers, Professor of Epidemiology; Dr. Ralph Frankowski, Professor of Biometry; and Dr. R. Sue McPherson, Assistant Professor of Epidemiology. The required number of courses was completed prior to taking the doctoral qualifying exam under the supervision of the advisory committee. The principal investigator attended the 30th Annual Meeting for the Society for Epidemiologic Research, held from June 12 - 14, 1997 in Edmonton, Alberta, Canada. The qualifying examination was completed satisfactorily in August, 1997, permitting admission to candidacy for a doctoral degree (see Appendix A-3).

Year 02: Completed Tasks: During the second performance period (September 1, 1997 - August 31, 1998) library research was conducted towards the Ph.D. proposal and dissertation, and data analysis was initiated. Dissertation research courses in

compliance with the UTSPH guidelines were taken, and additional courses were taken in 'Epidemiologic Design and Analysis', 'Causal Inference', and a one-day workshop on 'Molecular Epidemiology' (see below). Appendix A-3 shows the complete list of courses taken. A request to appoint a Ph.D. doctoral thesis committee was submitted in the Fall, 1997 and was approved. A revision was made to include Dr. Jonathan M. Samet, Professor and Chairman of Epidemiology at Johns Hopkins University, School of Hygiene and Public Health, who was the original Principal Investigator of the 'New Mexico Women's Health Study'. This revision was approved in April, 1998 (see Appendix A-3). Following approval of the doctoral thesis committee, a dissertation proposal was submitted to the advisory committee for approval and to the Associate Dean for Research (see Appendix A-1). Approval was granted in January, 1998 (see Appendix A-3). The principal investigator attended the 31th Annual Meeting for the Society for Epidemiologic Research, held from June 24 - 26, 1998 in Chicago, Illinois, and participated in the one-day sponsored "American College of Epidemiology/Society for Epidemiology Research" Workshop on "Genetic Fundamentals for Molecular Epidemiology" held June 23, 1998.

Year 03: Summary of Plans: The scope of work will be completed during the third and final performance period (September 1, 1998 - August 31, 1999), with the completion of data analyses, the doctoral dissertation, and a final report. The doctoral dissertation will be completed to meet the standards for an article submitted for publication to a peer-reviewed journal.

An outline of aims to be investigated for completion of data analyses is provided below. It is not exhaustive, and may change based on the results of on-going analyses and recommendations of the doctoral committee.

- Further evaluate whether the group of subjects who reported stopping alcohol consumption at the time of their diagnosis may have affected estimates for 'past' alcohol intake. Variables such as age at first alcohol use, amount at each age point, total lifetime average, and duration of drinking will be examined to determine if responses are significantly different from the remaining 'former' drinkers, and current drinkers.

- Define 'lifetime' alcohol exposure based on reported intake at ages 25, 35, and 50 and the subject's age.
- Evaluate whether subjects who are former drinkers at each age point (25, 35, 50) should be recoded and considered as nondrinkers at a specific age point
- Perform conditional multivariate logistic regression analyses, adjusted for selected covariates, confounders, and effect modifiers, to calculate the odds ratios for the most appropriate alcohol exposure variables as measures of alcohol consumption and its association with breast cancer risk. Analyses will be performed for all subjects combined and stratified by ethnicity. Results of univariate analyses and the previous studies will be used as a guide in the selection of confounding variables for the multivariate final models.
- Determine whether to use alcohol exposure variables in a continuous or categorical form in the final modeling, and the best scale if used as a continuous measure.
- Evaluate the need to transform the FFQ variables, total energy and total fat, prior to their inclusion in models estimating the effect of 'recent' alcohol consumption.
- Energy-adjust the FFQ-based alcohol measures and total fat intake prior to inclusion in multivariate models, if necessary.
- Assess effect modification for models estimating 'past' and 'recent' alcohol consumption, by including product terms in the full models, if there is sufficient sample size. Full models (containing all covariates and any pertinent alcohol-covariate interactions) and restricted models will be compared using the log likelihood test statistic (75) to determine whether the interaction terms significantly contribute to an explanation of the variance in the outcome. Reduced models will be compared with main effects models to further evaluate any interaction terms found to be significant in the previous step.
- Investigate breast cancer as a polychotomous nominal outcome (hormone receptor-specific subtypes), adjusting for selected variables.
- Stratify univariate and multivariate analyses on menopausal status, if warranted and if sample size is sufficient. Menopausal status, as a marker for change in

endogenous hormones, may be a critical effect modifier of the association between alcohol and breast cancer, as shown in previous work by Longnecker et al. (13).

Table 1. Means and Standard Deviations (SD) for Continuous Variables, Stratified by Ethnicity and Case-Control Status, New Mexico Women's Health Study (NMWHS), 1992-1994

	Hispanic						non-Hispanic White					
	Cases			Controls			Cases			Controls		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age (years) †	332	52.50	11.68	388	52.40	11.42	380	54.67	10.35	456	52.45	11.98
Age at Menarche (years)	329	12.79	1.57	387	12.74	1.74	380	12.58	1.50	454	12.64	1.54
Age at 1st Full-term Birth (years)	294	21.60	4.38	358	21.42	4.26	320	23.51	5.05	383	23.03	5.00
Age at Menopause (years)	97	47.25	4.76	101	47.73	4.83	145	49.02	4.07	131	48.98	4.19
Age at 1st Intake of Alcohol (years)	249	22.02	7.47	306	20.85	7.74	306	20.20	6.95	329	19.04	5.73
Body Mass Index - 18y (kg/m2)	321	20.58	2.76	386	20.57	3.06	378	20.16	2.84	453	20.37	2.94
Body Mass Index - Usual (kg/m2)	328	25.65	4.70	381	24.64	4.29	378	22.97	3.96	454	23.21	3.94
Vigorous Physical Activity (METS/week)	332	13.65	23.81	388	22.41	29.09	380	20.29	24.31	456	22.70	24.31
Total Energy Intake (kcal/day)	326	2401.0	999.1	379	2412.0	953.2	377	2170.2	837.6	451	2325.2	846.5
Total Fat Intake (g/day)	326	91.91	44.90	379	93.27	42.38	377	84.74	40.83	451	91.46	41.53

Table 1. Means and Standard Deviations (SD) for Continuous Variables, Stratified by Ethnicity and Case-Control Status, New Mexico Women's Health Study (NMWHS), 1992-1994

	Hispanic						non-Hispanic White					
	Cases			Controls			Cases			Controls		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Recent Alcohol Intake (g/day from FFQ)	114	5.63	7.89	143	4.94	6.87	188	12.97	20.25	263	8.91	13.51
Duration of Alcohol Intake (years)	249	25.42	11.66	306	26.36	13.05	329	30.97	12.17	410	29.94	12.69
Drinks per Week at Age 25*	186	1.84	3.48	229	2.25	5.61	268	3.11	5.60	334	3.98	6.84
Drinks per Week at Age 35*	190	2.31	5.14	218	2.70	8.61	271	3.84	6.24	315	4.09	7.94
Drinks per Week at Age 50*	98	2.37	4.59	102	1.41	1.93	174	4.71	7.16	171	4.29	6.00

* Excludes non-drinkers (intake = 0) at each age. † age (based on date of diagnosis for cases, date of interview for controls.
Sample sizes vary among variables due to missing data or exclusions as indicated.
METS, metabolic equivalent; kcal, kilocalories; g, grams; kg/m2 (kilograms weight/meters height2)

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Age group (years)														
30-39	42	12.7	55	14.2	33	8.7	67	14.7	75	10.5	122	14.5	197	12.7
40-64	221	66.6	255	65.7	275	72.4	290	63.6	496	69.7	545	64.6	1041	66.9
65-74	69	20.8	78	20.1	72	18.9	99	21.7	141	19.8	177	21.0	318	20.4
Education														
< Highschool	104	31.3	86	22.2	24	6.3	29	6.4	128	18.0	115	13.6	243	15.6
Highschool	129	38.9	150	38.7	102	26.8	111	24.3	231	32.4	261	30.9	492	31.6
> Highschool	96	28.9	152	39.2	253	66.6	315	69.1	349	49.0	467	55.3	816	52.4
Missing	3	0.9	1	0.3	1	0.3	1	0.2	4	0.6	2	0.2	6	0.4
Income														
≤ $9,999	78	23.5	51	13.1	22	5.8	24	5.3	100	14.0	75	8.9	175	11.2
$10,000-$19,000	81	24.4	83	21.4	47	12.4	66	14.5	128	18.0	149	17.7	277	17.8
$20,000-$29,000	53	16.0	67	17.3	73	19.2	75	16.4	126	17.7	142	16.8	268	17.2
$30,000-$39,000	48	14.5	64	16.5	52	13.7	75	16.4	100	14.0	139	16.5	239	15.4
≥ $40,000	55	16.6	112	28.9	167	43.9	204	44.7	222	31.2	316	37.4	538	34.6
Missing	17	5.1	11	2.8	19	5.0	12	2.6	36	5.1	23	2.7	59	3.8
Marital status														
Ever-married	308	92.8	365	94.1	360	94.7	438	96.1	668	93.8	803	95.1	1471	94.5
Never-married	24	7.2	23	5.9	20	5.3	18	3.9	44	6.2	41	4.9	85	5.5

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Age at menarche (years)														
≤ 12	133	40.1	170	43.8	185	48.7	211	46.3	318	44.7	381	45.1	699	44.9
13	101	30.4	109	28.1	111	29.2	140	30.7	212	29.8	249	29.5	461	29.6
≥ 14	95	28.6	108	27.8	84	22.1	103	22.6	179	25.1	211	25.0	390	25.1
Missing	3	0.9	1	0.3	0	0.0	2	0.4	3	0.4	3	0.4	6	0.4
Menopausal status (based on coding shown below)*														
Premenopausal	131	39.5	154	39.7	116	30.5	186	40.8	247	34.7	340	40.3	587	37.7
Post-menopausal	178	53.6	219	56.4	239	62.9	249	54.6	417	58.6	468	55.5	885	56.9
Surgical unknown	21	6.3	14	3.6	24	6.3	21	4.6	45	6.3	35	4.1	80	5.1
Missing	2	0.6	1	0.3	1	0.3	0	0.0	3	0.4	1	0.1	4	0.3
Menopausal status														
Premenopausal	120	36.1	148	38.1	110	28.9	176	38.6	230	32.3	324	38.4	554	35.6
Post-natural menopause	97	29.2	101	26.0	145	38.2	131	28.7	242	34.0	232	27.5	474	30.5
Post-surgical menopause	50	15.1	76	19.6	71	18.7	94	20.6	121	17.0	170	20.1	291	18.7
Surgical unknown	21	6.3	14	3.6	24	6.3	21	4.6	45	6.3	35	4.1	80	5.1
Surgical Unknown < 44	11	3.3	6	1.5	6	1.6	10	2.2	17	2.4	16	1.9	33	2.1
Surgical Unknown > 54	31	9.3	42	10.8	23	6.1	24	5.3	54	7.6	66	7.8	120	7.7
Unknown	2	0.6	1	0.3	1	0.3	0	0.0	3	0.4	1	0.1	4	0.3

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Age at natural menopause (years)														
≤ 44	19	19.6	19	18.8	24	16.6	22	16.8	43	17.8	41	17.7	84	17.7
45-49	41	42.3	41	40.6	44	30.3	45	34.4	85	35.1	86	37.1	171	36.1
50-51	26	26.8	24	23.8	43	29.7	31	23.7	69	28.5	55	23.7	124	26.2
≥ 52	11	11.3	17	16.8	34	23.4	33	25.2	45	18.6	50	21.6	95	20
Subtotal	97		101		145		131		242		232		474	
Age at first full-term birth (years)														
Nulliparous	38	11.4	30	7.7	60	15.8	73	16.0	98	13.8	103	12.2	201	12.9
≤ 18	71	21.4	89	22.9	43	11.3	67	14.7	114	16.0	156	18.5	270	17.4
19-20	71	21.4	94	24.2	60	15.8	73	16.0	131	18.4	167	19.8	298	19.2
21-22	50	15.1	64	16.5	59	15.5	64	14.0	109	15.3	128	15.2	237	15.2
23-26	62	18.7	68	17.5	82	21.6	95	20.8	144	20.2	163	19.3	307	19.7
≥ 27	40	12.0	43	11.1	76	20.0	84	18.4	116	16.3	127	15.0	243	15.6
Number of full-term births														
Nulliparous	38	11.4	30	7.7	60	15.8	73	16.0	98	13.8	103	12.2	201	12.9
1	29	8.7	35	9.0	63	16.6	58	12.7	92	12.9	93	11.0	185	11.9
2	66	19.9	98	25.3	128	33.7	138	30.3	194	27.2	236	28.0	430	27.6
3	80	24.1	72	18.6	66	17.4	101	22.1	146	20.5	173	20.5	319	20.5
≥ 4	119	35.8	153	39.4	63	16.6	86	18.9	182	25.6	239	28.3	421	27.1

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Duration of Lactation (months)														
Nulliparous	38	11.4	30	7.7	60	15.8	73	16.0	98	13.8	103	12.2	201	12.9
Parous, 1-12 months	109	32.8	128	33.0	167	43.9	157	34.4	276	38.8	285	33.8	561	36.1
Parous, >12 months	52	15.7	82	21.1	43	11.3	99	21.7	95	13.3	181	21.4	276	17.7
Parous, never	133	40.1	145	37.4	110	28.9	125	27.4	243	34.1	270	32.0	513	33.0
Missing	0	0.0	3	0.8	0	0.0	2	0.4	0	0.0	5	0.6	5	0.3
Benign breast disease														
Yes	45	13.6	40	10.3	95	25.0	77	16.9	140	19.7	117	13.9	257	16.5
No	274	82.5	348	89.7	268	70.5	375	82.2	542	76.1	723	85.7	1265	81.3
Missing	13	3.9	0	0.0	17	4.5	4	0.9	30	4.2	4	0.5	34	2.2
Estrogen														
Yes	112	33.7	163	42.0	200	52.6	214	46.9	312	43.8	377	44.7	689	44.3
No	218	65.7	224	57.7	180	47.4	239	52.4	398	55.9	463	54.9	861	55.3
Missing	2	0.6	1	0.3	0	0.0	3	0.7	2	0.3	4	0.5	6	0.4
Progesterone														
No	296	89.2	334	86.1	274	72.1	364	79.8	570	80.1	698	82.7	1268	81.5
Yes	36	10.8	54	13.9	106	27.9	92	20.2	142	19.9	146	17.3	288	18.5
Oral contraceptive use														
No	149	44.9	146	37.6	146	38.4	155	34.0	295	41.4	301	35.7	596	38.3
Yes	183	55.1	242	62.4	234	61.6	301	66.0	417	58.6	543	64.3	960	61.7

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Oral contraceptives, duration (years)														
Never used	149	44.9	146	37.6	146	38.4	155	34.0	295	41.4	301	35.7	596	38.3
≤ 1 y	59	17.8	82	21.1	80	21.1	67	14.7	139	19.5	149	17.7	288	18.5
2 to 5.00	54	16.3	75	19.3	67	17.6	114	25.0	121	17.0	189	22.4	310	19.9
> 5.01	67	20.2	84	21.6	83	21.8	118	25.9	150	21.1	202	23.9	352	22.6
Missing	3	0.9	1	0.3	4	1.1	2	0.4	7	1.0	3	0.4	10	0.6
Body Mass Index at age 18 (kg/m2)														
≤ 18.56	75	22.6	87	22.4	93	24.5	127	27.9	168	23.6	214	25.4	382	24.6
< 18.57-20.08	71	21.4	108	27.8	112	29.5	102	22.4	183	25.7	210	24.9	393	25.3
< 20.08-21.94	103	31.0	92	23.7	110	28.9	121	26.5	213	29.9	213	25.2	426	27.4
> 21.94	72	21.7	99	25.5	63	16.6	103	22.6	135	19.0	202	23.9	337	21.7
Missing	11	3.3	2	0.5	2	0.5	3	0.7	13	1.8	5	0.6	18	1.2
Usual Body Mass Index (kg/m2)														
≤ 21.09	35	10.5	75	19.3	119	31.3	134	29.4	154	21.6	209	24.8	363	23.3
< 21.10-23.02	65	19.6	73	18.8	126	33.2	132	28.9	191	26.8	205	24.3	396	25.4
< 23.03-25.68	95	28.6	109	28.1	68	17.9	103	22.6	163	22.9	212	25.1	375	24.1
> 25.68	133	40.1	124	32.0	65	17.1	85	18.6	198	27.8	209	24.8	407	26.2
Missing	4	1.2	7	1.8	2	0.5	2	0.4	6	0.8	9	1.1	15	1.0
Smoking, greater than 6 months														
Yes	145	43.7	186	47.9	185	48.7	240	52.6	330	46.3	426	50.5	756	48.6
No	187	56.3	202	52.1	195	51.3	216	47.4	382	53.7	418	49.5	800	51.4

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Family history of breast disease														
No	292	88.0	352	90.7	317	83.4	402	88.2	609	85.5	754	89.3	1363	87.6
Yes	40	12.0	36	9.3	63	16.6	54	11.8	103	14.5	90	10.7	193	12.4
Energy Intake (kcals)														
≤ 1606.31	68	20.5	87	22.4	105	27.6	79	17.3	173	24.3	166	19.7	339	21.8
1606.32 to 2017.06	59	17.8	58	14.9	86	22.6	108	23.7	145	20.4	166	19.7	311	20.0
2017.07 to 2435.52	72	21.7	71	18.3	68	17.9	95	20.8	140	19.7	166	19.7	306	19.7
2435.52 to 3031.63	56	16.9	79	20.4	59	15.5	87	19.1	115	16.2	166	19.7	281	18.1
> 3031.63	71	21.4	84	21.6	59	15.5	82	18.0	130	18.3	166	19.7	296	19.0
Missing	6	1.8	9	2.3	3	0.8	5	1.1	9	1.3	14	1.7	23	1.5
Total Fat Intake (grams)														
≤ 57.44	75	22.6	80	20.6	106	27.9	86	18.9	181	25.4	166	19.7	347	22.3
57.45 to 74.70	64	19.3	62	16.0	89	23.4	104	22.8	153	21.5	166	19.7	319	20.5
74.71 to 95.37	63	19.0	78	20.1	67	17.6	88	19.3	130	18.3	166	19.7	296	19.0
95.38 to 122.56	57	17.2	82	21.1	53	13.9	84	18.4	110	15.4	166	19.7	276	17.7
> 122.56	67	20.2	77	19.8	62	16.3	89	19.5	129	18.1	166	19.7	295	19.0
Missing	6	1.8	9	2.3	3	0.8	5	1.1	9	1.3	14	1.7	23	

Table 2. Participant Characteristics, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Vigorous Physical Activity (METS)														
none or non-vigorous	148	44.6	106	27.3	108	28.4	87	19.1	256	36.0	193	22.9	449	28.9
light, 0 to 12.5	92	27.7	110	28.4	95	25.0	142	31.1	187	26.3	252	29.9	439	28.2
moderate, 12.6 to 35	47	14.2	76	19.6	104	27.4	118	25.9	151	21.2	194	23.0	345	22.2
heavy, > 35	45	13.6	96	24.7	73	19.2	109	23.9	118	16.6	205	24.3	323	20.8

* Post-natural and surgical menopause combined; surgical unknowns recoded to premenopausal or postmenopausal based on age <10th percentile (43yrs) or >90th percentile (54yrs)

METS, metabolic equivalents

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Alcohol consumption														
No	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
Yes	249	75.0	306	78.9	329	86.6	410	89.9	578	81.2	716	84.8	1294	83.2
Alcohol consumption														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
Current drinkers	166	50.0	230	59.3	233	61.3	328	71.9	399	56.0	558	66.1	957	61.5
Former drinkers	83	25.0	76	19.6	96	25.3	82	18.0	179	25.1	158	18.7	337	21.7
Age at first use of alcohol (years)														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
≤ 16	40	12.0	63	16.2	72	18.9	120	26.3	112	15.7	183	21.7	295	19.0
17 to 18	47	14.2	70	18.0	94	24.7	117	25.7	141	19.8	187	22.2	328	21.1
19 to 21	72	21.7	88	22.7	95	25.0	102	22.4	167	23.5	190	22.5	357	22.9
≥ 22	90	27.1	85	21.9	68	17.9	71	15.6	158	22.2	156	18.5	314	20.2
Years since last alcohol consumption														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
0	21	6.3	2	0.5	23	6.1	3	0.7	44	6.2	5	0.6	49	3.1
1	7	2.1	4	1.0	9	2.4	3	0.7	16	2.2	7	0.8	23	1.5
2-4	11	3.3	7	1.8	13	3.4	10	2.2	24	3.4	17	2.0	41	2.6
5-14	18	5.4	14	3.6	24	6.3	32	7.0	42	5.9	46	5.5	88	5.7
≥ 15	25	7.5	48	12.4	27	7.1	34	7.5	52	7.3	82	9.7	134	8.6
Current drinker	166	50.0	230	59.3	233	61.3	328	71.9	399	56.0	558	66.1	957	61.5

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Duration of drinking (years)														
Nondrinkers	84	25.3	83	21.4	52	13.7	46	10.1	136	19.1	129	15.3	265	17.0
< 10	20	6.0	32	8.2	16	4.2	21	4.6	36	5.1	53	6.3	89	5.7
10 to 39	201	60.5	224	57.7	230	60.5	286	62.7	431	60.5	510	60.4	941	60.5
≥ 40	27	8.1	49	12.6	82	21.6	103	22.6	109	15.3	152	18.0	261	16.8
Intake at age 25														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
Drinkers	186	56.0	229	59.0	268	70.5	334	73.2	454	63.8	563	66.7	1017	65.4
Former drinkers	13	3.9	29	7.5	19	5.0	37	8.1	32	4.5	66	7.8	98	6.3
Drank at later ages	40	12.0	37	9.5	36	9.5	30	6.6	76	10.7	67	7.9	143	9.2
Current drinkers - no data	10	3.0	11	2.8	6	1.6	9	2.0	16	2.2	20	2.4	36	2.3
Frequency of drinking, age 25														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
Daily	3	0.9	10	2.6	27	7.1	22	4.8	30	4.2	32	3.8	62	4.0
Weekly	53	16.0	61	15.7	91	23.9	146	32.0	144	20.2	207	24.5	351	22.6
Monthly	66	19.9	79	20.4	78	20.5	94	20.6	144	20.2	173	20.5	317	20.4
Yearly	64	19.3	79	20.4	72	18.9	72	15.8	136	19.1	151	17.9	287	18.4
Former drinkers	13	3.9	29	7.5	19	5.0	37	8.1	32	4.5	66	7.8	98	6.3
Drank at later ages	40	12.0	37	9.5	36	9.5	30	6.6	76	10.7	67	7.9	143	9.2
Current drinkers - no data	10	3.0	10	2.6	6	1.6	9	2.0	16	2.2	19	2.3	35	2.2

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Gram intake/week, age 25														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
< 7.99	107	32.2	130	33.5	112	29.5	126	27.6	219	30.8	256	30.3	475	30.5
8.00 - 21.20	27	8.1	30	7.7	44	11.6	45	9.9	71	10.0	75	8.9	146	9.4
≥ 21.20	52	15.7	69	17.8	112	29.5	163	35.7	164	23.0	232	27.5	396	25.4
Former drinkers	13	3.9	29	7.5	19	5.0	37	8.1	32	4.5	66	7.8	98	6.3
Drank at later ages	40	12.0	37	9.5	36	9.5	30	6.6	76	10.7	67	7.9	143	9.2
Current drinkers - no data	10	3.0	11	2.8	6	1.6	9	2.0	16	2.2	20	2.4	36	2.3
Drinks per week, age 25														
Nondrinkers	83	25.0	82	21.1	51	13.4	46	10.1	134	18.8	128	15.2	262	16.8
≤ 0.9	123	37.0	153	39.4	136	35.8	155	34.0	259	36.4	308	36.5	567	36.4
1.0 to 2.9	24	7.2	26	6.7	46	12.1	48	10.5	70	9.8	74	8.8	144	9.3
3.0 to 5.9	18	5.4	22	5.7	31	8.2	59	12.9	49	6.9	81	9.6	130	8.4
≥ 6.0	21	6.3	28	7.2	55	14.5	72	15.8	76	10.7	100	11.8	176	11.3
Former drinkers	13	3.9	29	7.5	19	5.0	37	8.1	32	4.5	66	7.8	98	6.3
Drank at later ages	40	12.0	37	9.5	36	9.5	30	6.6	76	10.7	67	7.9	143	9.2
Current drinkers - no data	10	3.0	11	2.8	6	1.6	9	2.0	16	2.2	20	2.4	36	2.3
Intake at age 35 *														
Nondrinkers	83	25.0	79	20.4	50	13.2	45	9.9	133	18.7	124	14.7	257	16.5
Current drinkers	188	56.6	218	56.2	270	71.1	315	69.1	458	64.3	533	63.2	991	63.7
Former drinkers	24	7.2	43	11.1	34	8.9	49	10.7	58	8.1	92	10.9	150	9.6
Drank at later ages	13	3.9	12	3.1	13	3.4	10	2.2	26	3.7	22	2.6	48	3.1
Current drinkers - no data	9	2.7	9	2.3	4	1.1	7	1.5	13	1.8	16	1.9	29	1.9

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Frequency of drinking, age 35 *														
Nondrinkers	83	25.0	79	20.4	50	13.2	45	9.9	133	18.7	124	14.7	257	16.5
Daily	5	1.5	16	4.1	36	9.5	25	5.5	41	5.8	41	4.9	82	5.3
Weekly	57	17.2	57	14.7	101	26.6	136	29.8	158	22.2	193	22.9	351	22.6
Monthly	59	17.8	70	18.0	69	18.2	97	21.3	128	18.0	167	19.8	295	19.0
Yearly	67	20.2	75	19.3	64	16.8	57	12.5	131	18.4	132	15.6	263	16.9
Former drinkers	24	7.2	43	11.1	34	8.9	49	10.7	58	8.1	92	10.9	150	9.6
Drank at later ages	13	3.9	12	3.1	13	3.4	10	2.2	26	3.7	22	2.6	48	3.1
Current drinkers - no data	9	2.7	9	2.3	4	1.1	7	1.5	13	1.8	16	1.9	29	1.9
Gram intake/week, age 35 *														
Nondrinkers	83	25.0	79	20.4	50	13.2	45	9.9	133	18.7	124	14.7	257	16.5
< 7.99	101	30.4	113	29.1	102	26.8	116	25.4	203	28.5	229	27.1	432	27.8
8.00 - 21.19	25	7.5	32	8.2	41	10.8	50	11.0	66	9.3	82	9.7	148	9.5
≥ 21.20	62	18.7	73	18.8	127	33.4	149	32.7	189	26.5	222	26.3	411	26.4
Former drinkers	24	7.2	43	11.1	34	8.9	49	10.7	58	8.1	92	10.9	150	9.6
Drank at later ages	13	3.9	12	3.1	13	3.4	10	2.2	26	3.7	22	2.6	48	3.1
Current drinkers - no data	9	2.7	9	2.3	4	1.1	7	1.5	13	1.8	16	1.9	29	1.9
Drinks per week, age 35*														
Nondrinkers	83	25.0	79	20.4	50	13.2	45	9.9	133	18.7	124	14.7	257	16.5
≤ 0.9	115	34.6	130	33.5	121	31.8	143	31.4	236	33.1	273	32.3	509	32.7
1.0 to 2.9	28	8.4	37	9.5	50	13.2	50	11.0	78	11.0	87	10.3	165	10.6
3.0 to 5.9	23	6.9	23	5.9	35	9.2	60	13.2	58	8.1	83	9.8	141	9.1
≥ 6.0	22	6.6	28	7.2	64	16.8	62	13.6	86	12.1	90	10.7	176	11.3
Former drinkers	24	7.2	43	11.1	34	8.9	49	10.7	58	8.1	92	10.9	150	9.6
Drank at later ages	13	3.9	12	3.1	13	3.4	10	2.2	26	3.7	22	2.6	48	3.1
Current drinkers - no data	9	2.7	9	2.3	4	1.1	7	1.5	13	1.8	16	1.9	29	1.9

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Intake at age 50 *														
Nondrinkers	59	17.8	60	15.5	44	11.6	33	7.2	103	14.5	93	11.0	196	12.6
Current drinkers	93	28.0	102	26.3	170	44.7	171	37.5	263	36.9	273	32.3	536	34.4
Former drinkers	28	8.4	41	10.6	42	11.1	31	6.8	70	9.8	72	8.5	142	9.1
Drank at later ages	2	0.6	4	1.0	3	0.8	1	0.2	5	0.7	5	0.6	10	0.6
Current drinkers - no data	3	0.9	2	0.5	2	0.5	4	0.9	5	0.7	6	0.7	11	0.7
Frequency of drinking, age 50 *														
Nondrinkers	59	17.8	60	15.5	44	11.6	33	7.2	103	14.5	93	11.0	196	12.6
Daily	4	1.2	7	1.8	34	8.9	37	8.1	38	5.3	44	5.2	82	5.3
Weekly	23	6.9	32	8.2	59	15.5	61	13.4	82	11.5	93	11.0	175	11.2
Monthly	29	8.7	28	7.2	36	9.5	39	8.6	65	9.1	67	7.9	132	8.5
Yearly	37	11.1	35	9.0	41	10.8	34	7.5	78	11.0	69	8.2	147	9.4
Former drinkers	28	8.4	41	10.6	42	11.1	31	6.8	70	9.8	72	8.5	142	9.1
Drank at later ages	2	0.6	4	1.0	3	0.8	1	0.2	5	0.7	5	0.6	10	0.6
Current drinkers - no data	3	0.9	2	0.5	2	0.5	4	0.9	5	0.7	6	0.7	11	0.7
Gram intake/week, age 50 *														
Nondrinkers	59	17.8	60	15.5	44	11.6	33	7.2	103	14.5	93	11.0	196	12.6
< 7.99	51	15.4	47	12.1	59	15.5	50	11.0	110	15.4	97	11.5	207	13.3
8.00 - 21.19	17	5.1	25	6.4	25	6.6	32	7.0	42	5.9	57	6.8	99	6.4
≥ 21.20	25	7.5	30	7.7	86	22.6	89	19.5	111	15.6	119	14.1	230	14.8
Former drinkers	28	8.4	41	10.6	42	11.1	31	6.8	70	9.8	72	8.5	142	9.1
Drank at later ages	2	0.6	4	1.0	3	0.8	1	0.2	5	0.7	5	0.6	10	0.6
Current drinkers - no data	3	0.9	2	0.5	2	0.5	4	0.9	5	0.7	6	0.7	11	0.7

Table 3. Prevalences of Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic White				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Drinks per week, age 50 *														
Nondrinkers	59	17.8	60	15.5	44	11.6	33	7.2	103	14.5	93	11.0	196	12.6
≤ 0.5	48	14.5	39	10.1	51	13.4	44	9.6	99	13.9	83	9.8	182	11.7
0.5 to 0.9	9	2.7	21	5.4	20	5.3	21	4.6	29	4.1	42	5.0	71	4.6
1.0 to 5.9	23	6.9	36	9.3	49	12.9	59	12.9	72	10.1	95	11.3	167	10.7
≥ 6.0	13	3.9	6	1.5	50	13.2	47	10.3	63	8.8	53	6.3	116	7.5
Former drinkers	28	8.4	41	10.6	42	11.1	31	6.8	70	9.8	72	8.5	142	9.1
Drank at later ages	2	0.6	4	1.0	3	0.8	1	0.2	5	0.7	5	0.6	10	0.6
Current drinkers - no data	3	0.9	2	0.5	2	0.5	4	0.9	5	0.7	6	0.7	11	0.7
Alcohol Intake (g/day) from FFQ†														
None	212	63.9	236	60.8	189	49.7	188	41.2	401	56.3	424	50.2	825	53.0
≤ 5.99	82	24.7	108	27.8	97	25.5	158	34.6	179	25.1	266	31.5	445	28.6
6.00 to 21.20	26	7.8	30	7.7	53	13.9	78	17.1	79	11.1	108	12.8	187	12.0
> 21.20	12	3.6	14	3.6	41	10.8	32	7.0	53	7.4	46	5.5	99	6.4

g, grams; FFQ, Food Frequency Questionnaire

* Numbers are reduced to compared categories of drinking with non-drinkers 35 y and 50 y, respectively, at ages 35 and 50

† Absolute intake.

Table 4. Co-Morbid Conditions, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total					
	Cases		Controls		Cases		Controls		Cases		Controls		TOTAL	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	332		388		380		456		712		844		1556	
Non-Insulin Dependent Diabetes (missing =1)														
Yes	46	13.9	40	10.3	14	3.7	17	3.7	60	8.4	57	6.8	117	7.5
No	286	86.1	348	89.7	366	96.3	438	96.1	652	91.6	786	93.1	1438	92.4
High Blood Pressure (missing = 1)														
Yes	104	31.3	97	25.0	117	30.8	119	26.1	221	31.0	216	25.6	437	28.1
No	228	68.7	291	75.0	262	68.9	337	73.9	490	68.8	628	74.4	1118	71.9
Gallbladder Disease (missing =2)														
Yes	60	18.1	74	19.1	48	12.6	58	12.7	108	15.2	132	15.6	240	15.4
No	271	81.6	314	80.9	332	87.4	397	87.1	603	84.7	711	84.2	1314	84.4
Hypercholesterolemia (missing = 8)														
Yes	83	25.0	102	26.3	106	27.9	115	25.2	189	26.5	217	25.7	406	26.1
No	245	73.8	285	73.5	271	71.3	341	74.8	516	72.5	626	74.2	1142	73.4
Rheumatoid Arthritis (missing = 5)														
Yes	37	11.1	44	11.3	24	6.3	23	5.0	61	8.6	67	7.9	128	8.2
No	293	88.3	344	88.7	356	93.7	430	94.3	649	91.2	774	91.7	1423	91.5
Thyroid Disease (missing = 11)														
Yes, hyperthyroid	18	5.4	15	3.9	20	5.3	16	3.5	38	5.3	31	3.7	69	4.4
Yes, hypothyroid	37	11.1	42	10.8	66	17.4	86	18.9	103	14.5	128	15.2	231	14.8
Yes, other	10	3.0	10	2.6	24	6.3	24	5.3	34	4.8	34	4.0	68	4.4
No	264	79.5	320	82.5	265	69.7	328	71.9	529	74.3	648	76.8	1177	75.6

Table 5. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Potential Risk Factors of Breast Cancer, Stratified by Ethnicity and Case-Control Status

	Hispanic				Non-Hispanic White				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI
Education												
< Highschool	104	86	1.47	0.99-2.18	24	29	0.88	0.48-1.64	128	115	1.25	0.90-1.73
Highschool	129	150	1.00	---	102	111	1.00	---	231	261	1.00	---
> Highschool	96	152	0.68	0.47-0.97	253	315	0.89	0.64-1.25	349	467	0.80	0.63-1.02
Income												
≤ $9,999	78	51	2.05	1.21-3.50	22	24	0.97	0.49-1.91	100	75	1.53	1.02-2.28
$10,000-$19,000	81	83	1.28	0.79-2.08	47	66	0.72	0.43-1.19	128	149	0.97	0.69-1.37
$20,000-$29,000	53	67	1.00	---	73	75	1.00	---	126	142	1.00	---
$30,000-$39,000	48	64	0.91	0.54-1.54	52	75	0.75	0.46-1.23	100	139	0.82	0.57-1.17
≥ $40,000	55	112	0.60	0.37-0.98	167	204	0.90	0.60-1.34	222	316	0.77	0.57-1.05
Marital status												
Never-married	24	23	1.00	---	20	18	1.00	---	44	41	1.00	---
Ever-married	308	365	0.81	0.44-1.51	360	438	0.74	0.37-1.45	668	803	0.73	0.46-1.14
Age at menarche (years)												
≤ 12	133	170	0.88	0.60-1.28	185	211	1.15	0.80-1.64	318	381	1.03	0.80-1.33
13	101	109	1.08	0.72-1.61	111	140	1.03	0.70-1.53	212	249	1.05	0.80-1.39
≥ 14	95	108	1.00	---	84	103	1.00	---	179	211	1.00	---
Menopausal status												
Premenopausal	131	154	1.00	---	116	186	1.00	---	247	340	1.00	---
Post-menopausal	178	219	1.18	0.67-2.08	239	249	0.86	0.51-1.48	417	468	0.95	0.64-1.40
Surgical Unknown	21	14	1.80	0.85-3.80	24	21	1.43	0.74-2.78	45	35	1.51	0.92-2.47

Table 5. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Potential Risk Factors of Breast Cancer, Stratified by Ethnicity and Case-Control Status

	Hispanic				Non-Hispanic White				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI
Age at natural menopause (years)												
≤ 44	19	19	1.00	---	24	22	1.00	---	43	41	1.00	---
45-49	41	41	0.90	0.39-2.07	44	45	0.82	0.40-1.70	85	86	0.89	0.52-1.54
50-51	26	24	1.08	0.42-2.74	43	31	1.11	0.52-2.37	69	55	1.08	0.60-1.94
≥ 52	11	17	0.84	0.28-2.49	34	33	0.86	0.39-1.90	45	50	0.88	0.47-1.65
Subtotal	97	101			145	131			242	232		
Age at first full-term birth (years)												
≤ 18	71	89	1.00	---	43	67	1.00	---	114	156	1.00	---
19-20	71	94	1.02	0.65-1.59	60	73	1.19	0.71-2.01	131	167	1.11	0.79-1.56
21-22	50	64	1.04	0.64-1.71	59	64	1.32	0.77-2.45	109	128	1.17	0.82-1.68
23-26	62	68	1.14	0.70-1.84	82	95	1.33	0.81-2.18	144	163	1.23	0.88-1.73
≥ 27	40	43	1.23	0.71-2.13	76	84	1.53	0.94-2.60	116	127	1.36	0.95-1.96
Nulliparous	38	30	1.54	0.85-2.77	60	73	1.30	0.77-2.22	98	103	1.36	0.93-1.99
Number of full-term births												
Nulliparous	38	30	1.46	0.83-2.57	60	73	1.33	0.81-2.19	98	103	1.37	0.95-1.96
1	29	35	0.99	0.55-1.79	63	58	1.90	1.13-3.17	92	93	1.51	1.03-2.19
2	66	98	0.78	0.51-1.20	128	138	1.56	1.02-2.40	194	236	1.21	0.90-1.62
3	80	72	1.43	0.93-2.18	66	101	0.94	0.59-1.50	146	173	1.17	0.86-1.60
≥ 4	119	153	1.00	---	63	86	1.00	---	182	239	1.00	---

Table 5. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Potential Risk Factors of Breast Cancer, Stratified by Ethnicity and Case-Control Status

	Hispanic				Non-Hispanic White				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI
Duration of Lactation (months)												
Nulliparous	38	30	1.30	0.75-2.26	60	73	0.96	0.62-1.51	98	103	1.30	0.75-2.26
Parous, 1-12 months	109	128	0.93	0.65-1.34	167	157	1.24	0.88-1.76	276	285	0.93	0.65-1.34
Parous, >12 months	52	82	0.68	0.44-1.06	43	99	0.53	0.34-0.84	95	181	0.68	0.44-1.06
Parous, never	133	145	1.00	---	110	125	1.00	---	243	270	1.00	---
Benign breast disease												
No	274	348	1.00	---	268	375	1.00	---	542	723	1.00	---
Yes	45	40	1.31	0.83-2.09	95	77	1.68	1.18-2.39	140	117	1.52	1.15-2.01
Oral contraceptives, duration (years)												
Never used	149	146	1.00	---	146	155	1.00	---	295	301	1.00	---
≤ 1 y	59	82	0.71	0.46-1.09	80	67	1.32	0.85-2.06	139	149	0.94	0.69-1.28
2 to 5.00	54	75	0.61	0.38-0.98	67	114	0.76	0.48-1.19	121	189	0.64	0.47-0.89
> 5.01	67	84	0.70	0.45-1.09	83	118	0.86	0.56-1.32	150	202	0.74	0.55-1.01
Missing	3	1			4	2			7	3		
Body Mass Index at age 18 (kg/m2)												
≤ 18.56	75	87	1.00	---	93	127	1.00	---	168	214	1.00	---
< 18.57-20.08	71	108	0.77	0.50-1.20	112	102	1.46	0.99-2.15	183	210	1.11	0.84-1.48
< 20.08-21.94	103	92	1.31	0.85-2.00	110	121	1.21	0.82-1.77	213	213	1.27	0.95-1.68
> 21.94	72	99	0.87	0.56-1.36	63	103	0.86	0.56-1.31	135	202	0.87	0.64-1.18

Table 5. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Potential Risk Factors of Breast Cancer, Stratified by Ethnicity and Case-Control Status

	Hispanic				Non-Hispanic White				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI
Usual Body Mass Index (kg/m2)												
≤ 21.09	35	75	1.00	---	119	134	1.00	---	154	209	1.00	---
<21.10-23.02	65	73	1.88	1.11-3.20	126	132	1.05	0.73-1.50	191	205	1.24	0.93-1.66
<23.03-25.68	95	109	1.87	1.14-3.06	68	103	0.65	0.43-0.97	163	212	1.00	0.74-1.35
> 25.68	133	124	2.38	1.46-3.87	65	85	0.81	0.53-1.24	198	209	1.21	0.9-1.64
Smoking, greater than 6 months												
No	187	202	1.00	---	195	216	1.00	---	382	418	1.00	---
Yes	145	186	0.84	0.62-1.14	185	240	0.84	0.63-1.11	330	426	0.84	0.68-1.03
Family history of breast disease												
No	292	352	1.00	---	317	402	1.00	---	609	754	1.00	---
Yes	40	36	1.30	0.80-2.12	63	54	1.46	0.98-2.18	103	90	1.36	1.00-1.85
Energy Intake (kcals)												
≤ 1606.31	68	87	1.00	---	105	79	1.00	---	173	166	1.00	---
1606.32 to 2017.06	59	58	1.27	0.78-2.07	86	108	0.60	0.39-0.90	145	166	0.84	0.62-1.15
2017.07 to 2435.52	72	71	1.37	0.86-2.20	68	95	0.54	0.35-0.84	140	166	0.84	0.62-1.15
2435.52 to 3031.63	56	79	0.95	0.59-1.53	59	87	0.52	0.33-0.82	115	166	0.69	0.50-0.96
> 3031.63	71	84	1.08	0.68-1.71	59	82	0.55	0.35-0.87	130	166	0.78	0.57-1.07

Table 5. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Potential Risk Factors of Breast Cancer, Stratified by Ethnicity and Case-Control Status

	Hispanic				Non-Hispanic White				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI
Total Fat Intake (grams) †												
≤ 57.44	75	80	1.00	---	106	86	1.00	---	181	166	1.00	---
57.45 to 74.70	64	62	1.09	0.68-1.76	89	104	0.67	0.44-1.01	153	166	0.85	0.62-1.15
74.71 to 95.37	63	78	0.86	0.54-1.37	67	88	0.66	0.42-1.02	130	166	0.74	0.54-1.01
95.38 to 122.56	57	82	0.79	0.49-1.26	53	84	0.53	0.34-0.85	110	166	0.64	0.46-0.88
> 122.56	67	77	0.92	0.57-1.46	62	89	0.57	0.37-0.89	129	166	0.74	0.54-1.01
Vigorous Physical Activity (METS)												
none or non-vigorous	148	106	1.00	---	108	87	10.00	---	256	193	1.00	---
light, 0 to 12.5	92	110	0.62	0.42-0.90	95	142	0.55	0.37-0.81	187	252	0.58	0.45-0.76
moderate, 12.6 to 35	47	76	0.45	0.29-0.71	104	118	0.73	0.49-1.08	151	194	0.60	0.45-0.81
heavy, > 35	45	96	0.34	0.22-0.54	73	109	0.55	0.36-0.84	118	205	0.44	0.33-0.60

OR, odds ratios; CI, confidence interval; g, grams; FFQ, Food Frequency Questionnaire; METS, metabolic equivalents.

† Absolute intake, unadjusted for total energy or fat intake.

Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Alcohol consumption												
No	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
Yes	249	306	0.78	0.54-1.14	329	410	0.76	0.49-1.19	578	716	0.80	0.60-1.06
Alcohol consumption												
Nondrinkers	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
Current drinkers	166	230	0.69	0.46-1.02	233	328	0.67	0.43-1.06	399	558	0.70	0.52-0.94
Former drinkers	83	76	1.02	0.65-1.61	96	82	1.08	0.65-1.81	179	158	1.09	0.78-1.52
Alcohol consumption												
Non-drinkers	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
Current drinkers	166	230	0.70	0.47-1.05	233	328	0.68	0.43-1.08	399	558	0.71	0.53-0.95
Former drinkers	55	70	0.73	0.45-1.19	64	76	0.78	0.45-1.33	119	146	0.78	0.55-1.11
Stopped within reference year	21	2	9.98	2.22-44.85	23	3	8.17	2.23-29.94	44	5	8.90	3.38-23.44
Stop 1 y before reference year	7	4	2.01	0.55-7.26	9	3	2.53	0.63-10.22	16	7	2.38	0.93-6.10
Age at first use of alcohol (years)												
Non-drinker	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
≤ 16	37	61	0.55	0.32-0.96	62	119	0.55	0.32-0.94	99	180	0.56	0.39-0.82
17 to 18	42	69	0.53	0.31-0.91	87	116	0.70	0.42-1.17	129	185	0.67	0.47-0.95
19 to 21	63	87	0.67	0.42-1.08	83	98	0.76	0.45-1.27	146	185	0.74	0.53-1.04
≥ 22	79	83	0.94	0.60-1.48	65	71	0.80	0.47-1.38	144	154	0.88	0.62-1.24
Stopped within reference year	21	2	9.49	2.11-42.68	23	3	7.95	2.17-29.02	44	5	8.59	3.26-22.61
Stop 1 y before reference year	7	4	1.92	0.53-6.96	9	3	2.48	0.62-10.00	16	7	2.31	0.90-5.91

Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Years since last alcohol consumption												
Non-drinker	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
0	21	2	10.18	2.27-45.78	23	3	8.16	2.23-29.93	44	5	8.98	3.41-23.67
1	7	4	2.04	0.57-7.40	9	3	2.54	0.63-10.25	16	7	2.40	0.94-6.15
2-4	11	7	1.54	0.56-4.23	13	10	1.11	0.43-2.86	24	17	1.33	0.67-2.61
5-14	18	14	1.21	0.55-2.63	24	32	0.71	0.36-1.40	42	46	0.90	0.55-1.49
≥ 15	25	48	0.48	0.26-0.86	27	34	0.74	0.38-1.45	52	82	0.60	0.39-0.92
Current drinkers	166	230	0.72	0.48-1.07	233	328	0.69	0.43-1.08	399	558	0.72	0.54-0.97
Duration of drinking												
Non-drinker	84	83	1.00	---	52	46	1.00	---	136	129	1.00	---
< 10	20	32	0.64	0.33-1.23	16	21	0.80	0.36-1.77	36	53	0.74	0.45-1.22
10 to 39	201	224	0.92	0.61-1.36	230	286	0.85	0.53-1.37	431	510	0.89	0.66-1.20
≥ 40	27	49	0.51	0.27-0.94	82	103	0.59	0.35-0.99	109	152	0.63	0.43-0.92
Intake at age 25												
Nondrinkers	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
Current drinkers	186	229	0.78	0.53-1.15	268	334	0.77	0.49-1.22	454	563	0.79	0.59-1.06
Former drinkers	13	29	0.42	0.20-0.89	19	37	0.47	0.23-0.96	32	66	0.48	0.29-0.80
Drank at later ages	40	37	1.01	0.57-1.77	36	30	1.01	0.53-1.93	76	67	1.07	0.70-1.62
Current drinkers - no data	10	11	0.87	0.33-2.27	6	9	0.62	0.20-1.93	16	20	0.85	0.41-1.74

Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Frequency of drinking, age 25												
Nondrinkers	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
Daily	3	10	0.29	0.08-1.11	27	22	1.18	0.58-2.42	30	32	0.90	0.51-1.60
Weekly	53	61	0.84	0.50-1.40	91	146	0.62	0.37-1.02	144	207	0.68	0.48-0.97
Monthly	66	79	0.81	0.50-1.30	78	94	0.76	0.45-1.29	144	173	0.80	0.57-1.13
Yearly	64	79	0.78	0.49-1.25	72	72	0.96	0.56-1.65	136	151	0.88	0.62-1.24
Former drinkers	13	29	0.43	0.20-0.89	19	37	0.47	0.23-0.96	32	66	0.48	0.29-0.79
Drank at later ages	40	37	1.01	0.58-1.77	36	30	1.02	0.53-1.95	76	67	1.06	0.70-1.62
Current drinkers - no data	10	10	0.87	0.33-2.27	6	9	0.62	0.20-1.93	16	19	0.84	0.41-1.74
Gram intake/week, age 25												
Nondrinkers	83	82	1.00	---	51	46	1.00	---	134	128	1.00	---
< 7.99	107	130	0.80	0.52-1.22	112	126	0.85	0.52-1.40	219	256	0.84	0.61-1.16
8.00 - 21.20	27	30	0.83	0.45-1.56	44	45	0.89	0.58-1.35	71	75	0.89	0.58-1.35
≥ 21.20	52	69	0.72	0.44-1.20	112	163	0.67	0.49-0.96	164	232	0.69	0.47-1.05
Former drinkers	13	29	0.42	0.20-0.89	19	37	0.47	0.29-0.79	32	66	0.48	0.29-0.79
Drank at later ages	40	37	1.01	0.57-1.77	36	30	1.01	0.70-1.61	76	67	1.06	0.70-1.61
Current drinkers - no data	10	11	0.86	0.33-2.26	6	9	0.62	0.41-1.73	16	20	0.84	0.41-1.73
Drinks per week, age 25												
Nondrinkers	83	82	1.00		51	46	1.00		134	128	1.00	
≤ 0.9	123	153	0.77	0.51-1.17	136	155	0.84	0.52-1.36	259	308	0.82	0.60-1.12
1.0 to 2.9	24	26	0.85	0.44-1.64	46	48	0.88	0.49-1.59	70	74	0.89	0.58-1.36
3.0 to 5.9	18	22	0.86	0.42-1.77	31	59	0.49	0.27-0.90	49	81	0.60	0.38-0.93
≥ 6.0	21	28	0.68	0.34-1.34	55	72	0.80	0.46-1.41	76	100	0.75	0.50-1.13
Former drinkers	13	29	0.42	0.20-0.89	19	37	0.47	0.23-0.96	32	66	0.48	0.29-0.79
Drank at later ages	40	37	1.01	0.57-1.77	36	30	1.02	0.53-1.94	76	67	1.06	0.70-1.61
Current drinkers - no data	10	11	0.86	0.33-2.26	6	9	0.63	0.20-1.95	16	20	0.84	0.41-1.74

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Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Intake at age 35 *												
Nondrinkers	83	79	1.00	---	50	45	1.00	---	133	124	1.00	---
Current drinkers	188	218	0.77	0.52-1.15	270	315	0.77	0.49-1.22	458	533	0.82	0.61-1.10
Former drinkers	24	43	0.49	0.27-0.91	34	49	0.64	0.34-1.18	58	92	0.58	0.38-0.87
Drank at later ages	13	12	1.00	0.41-2.40	13	10	1.06	0.42-2.69	26	22	1.07	0.57-2.01
Current drinkers - no data	9	9	0.87	0.31-2.43	4	7	0.58	0.16-2.14	13	16	0.85	0.41-1.77
Frequency of drinking, age 35 *												
Nondrinkers	83	79	1.00	---	50	45	1.00	---	133	124	1.00	---
Daily	5	16	0.27	0.10-0.79	36	25	1.26	0.64-2.48	41	41	0.94	0.56-1.58
Weekly	57	57	0.92	0.56-1.52	101	136	0.67	0.41-1.11	158	193	0.77	0.54-1.08
Monthly	59	70	0.73	0.44-1.20	69	97	0.63	0.37-1.07	128	167	0.72	0.51-1.03
Yearly	67	75	0.83	0.52-1.33	64	57	1.01	0.58-1.76	131	132	0.96	0.68-1.37
Former drinkers	24	43	0.49	0.27-0.91	34	49	0.63	0.34-1.17	58	92	0.57	0.38-0.86
Drank at later ages	13	12	1.01	0.42-2.44	13	10	1.07	0.42-2.70	26	22	1.07	0.57-2.01
Current drinkers - no data	9	9	0.86	0.31-2.42	4	7	0.57	0.15-2.12	13	16	0.85	0.41-1.76
Gram intake/week, age 35 *												
Nondrinkers	83	79	1.00	---	50	45	1.00	---	133	124	1.00	---
< 7.99	101	113	0.81	0.52-1.25	102	116	0.79	0.47-1.30	203	229	0.86	0.62-1.19
8.00 - 21.19	25	32	0.67	0.36-1.27	41	50	0.73	0.40-1.33	66	82	0.74	0.49-1.12
≥ 21.20	62	73	0.77	0.47-1.24	127	149	0.77	0.47-1.26	189	222	0.81	0.58-1.12
Former drinkers	24	43	0.49	0.27-0.91	34	49	0.64	0.34-1.18	58	92	0.57	0.38-0.86
Drank at later ages	13	12	1.00	0.41-2.40	13	10	1.06	0.42-2.69	26	22	1.07	0.57-2.01
Current drinkers - no data	9	9	0.87	0.31-2.44	4	7	0.58	0.16-2.14	13	16	0.85	0.41-1.77

Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Drinks per week, age 35 *												
Nondrinkers	83	79	1.00	---	50	45	1.00	---	133	124	1.00	---
≤ 0.9	115	130	0.80	0.52-1.22	121	143	0.76	0.46-1.24	236	273	0.83	0.61-1.14
1.0 to 2.9	28	37	0.68	0.38-1.24	50	50	0.91	0.51-1.64	78	87	0.83	0.56-1.25
3.0 to 5.9	23	23	0.98	0.49-1.96	35	60	0.51	0.28-0.94	58	83	0.66	0.43-1.02
≥ 6.0	22	28	0.65	0.34-1.26	64	62	0.94	0.54-1.64	86	90	0.90	0.60-1.35
Former drinkers	24	43	0.49	0.27-0.91	34	49	0.63	0.34-1.18	58	92	0.57	0.38-0.86
Drank at later ages	13	12	1.01	0.42-2.43	13	10	1.06	0.42-2.67	26	22	1.07	0.57-2.00
Current drinkers - no data	9	9	0.86	0.31-2.42	4	7	0.58	0.16-2.16	13	16	0.86	0.41-1.78
Intake at age 50 *												
Nondrinkers	59	60	1.00	---	44	33	1.00	---	103	93	1.00	---
Current drinkers	93	102	0.87	0.53-1.43	170	171	0.68	0.41-1.15	263	273	0.94	0.69-1.29
Former drinkers	28	41	0.66	0.35-1.25	42	31	0.90	0.46-1.78	70	72	0.63	0.45-0.88
Drank at later ages	2	4	0.53	0.09-3.23	3	1	2.69	0.26-27.5	5	5	0.96	0.27-3.44
Current drinkers - no data	3	2	1.20	0.17-8.36	2	4	0.29	0.05-1.73	5	6	0.82	0.39-1.75
Frequency of drinking, age 50 *												
Nondrinkers	59	60	1.00	---	44	33	1.00	---	103	93	1.00	---
Daily	4	7	0.55	0.15-2.04	34	37	0.64	0.33-1.24	38	44	0.66	0.38-1.15
Weekly	23	32	0.72	0.37-1.41	59	61	0.66	0.36-1.19	82	93	0.70	0.45-1.07
Monthly	29	28	0.93	0.47-1.83	36	39	0.61	0.31-1.19	65	67	0.76	0.48-1.21
Yearly	37	35	1.04	0.56-1.95	41	34	0.86	0.45-1.68	78	69	0.98	0.63-1.53
Former drinkers	28	41	0.66	0.35-1.26	42	31	0.90	0.45-1.77	70	72	0.79	0.50-1.24
Drank at later ages	2	4	0.52	0.09-3.18	3	1	2.65	0.26-27.2	5	5	0.92	0.25-3.33
Current drinkers - no data	3	2	1.20	0.17-8.39	2	4	0.29	0.05-1.73	5	6	0.60	0.17-2.14

Table 6. Age-Adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposures Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Gram intake/week, age 50 *												
Nondrinkers	59	60	1.00	---	44	33	1.00	---	103	93	1.00	---
< 7.99	51	47	1.09	0.61-1.95	59	50	0.94	0.53-1.66	110	97	0.96	0.63-1.44
8.00 - 21.19	17	25	0.57	0.27-1.21	25	32	0.68	0.35-1.34	42	57	0.59	0.35-0.97
≥ 21.20	25	30	0.83	0.42-1.63	86	89	0.76	0.45-1.28	111	119	0.74	0.49-1.11
Former drinkers	28	41	0.66	0.35-1.26	42	31	0.70	0.42-1.18	70	72	0.79	0.50-1.25
Drank at later ages	2	4	0.54	0.09-3.27	3	1	2.74	0.28-28.00	5	5	0.93	0.26-3.37
Current drinkers - no data	3	2	1.21	0.17-8.42	2	4	0.45	0.13-1.61	5	6	0.61	0.17-2.15
Drinks per week, age 50 *												
Nondrinkers	59	60	1.00	---	44	33	1.00	---	103	93	1.00	---
≤ 0.5	48	39	1.26	0.69-2.31	51	44	0.81	0.44-1.52	99	83	1.18	0.80-1.76
0.5 to 0.9	9	21	0.36	0.15-0.90	20	21	0.64	0.29-1.40	29	42	0.71	0.42-1.21
1.0 to 5.9	23	36	0.57	0.29-1.12	49	59	0.58	0.31-1.06	72	95	0.75	0.50-1.11
≥ 6.0	13	6	2.29	0.78-6.69	50	47	0.73	0.39-1.36	63	53	1.14	0.72-1.81
Former drinkers	28	41	0.65	0.34-1.25	42	31	0.91	0.46-1.79	70	72	0.63	0.45-0.88
Drank at later ages	2	4	0.52	0.09-3.19	3	1	0.21	0.26-27.8	5	5	0.96	0.27-3.46
Current drinkers - no data	3	2	1.22	0.18-8.46	2	4	0.29	0.05-1.73	5	6	0.82	0.39-1.75
Alcohol Intake (g/day) from FFQ †												
None	212	236	1.00	---	189	188	1.00	---	401	424	1.00	---
≤ 5.99	82	108	0.83	0.58-1.18	97	158	0.61	0.44-0.86	179	266	0.72	0.56-0.91
6.00 to 21.20	26	30	0.94	0.53-1.66	53	78	0.68	0.45-1.03	79	108	0.77	0.55-1.08
> 21.20	12	14	0.94	0.42-2.12	41	32	1.31	0.78-2.21	53	46	1.23	0.80-1.89

OR, odds ratios; CI, confidence interval; y, year; g, grams; FFQ, Food Frequency Questionnaire

* Numbers are reduced due to exclusion of subjects who were < 35 y or < 50 y at each time point.

† Absolute intake.

Table 7. Multivariate-adjusted Odds Ratios* and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Alcohol consumption												
No	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
Yes	249	306	0.96	0.62-1.50	329	410	0.72	0.49-1.20	578	716	0.87	0.64-1.20
Alcohol consumption												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
Current drinkers	166	230	0.86	0.54-1.37	233	328	0.61	0.37-1.02	399	558	0.76	0.54-1.05
Former drinkers	83	76	1.17	0.70-1.97	96	82	1.10	0.62-1.94	179	158	1.17	0.81-1.70
Alcohol consumption												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
Current drinkers	166	230	0.88	0.55-1.40	233	328	0.63	0.38-1.05	399	558	0.77	0.56-1.08
Former drinkers	55	70	0.81	0.47-1.40	64	76	0.80	0.44-1.45	119	146	0.86	0.58-1.26
Stopped within reference year	21	2	11.19	2.38-52.7	23	3	8.01	2.06-31.2	44	5	8.90	3.29-21.1
Stop 1 y before reference year	7	4	3.56	0.81-15.6	9	3	2.02	0.46-8.81	16	7	2.48	0.89-6.86
Age at first use of alcohol (years)												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
≤ 16	37	61	0.72	0.38-1.37	62	119	0.53	0.29-0.97	99	180	0.65	0.43-0.99
17 to 18	42	69	0.61	0.33-1.12	87	116	0.63	0.35-1.12	129	185	0.70	0.47-1.04
19 to 21	63	87	0.82	0.47-1.43	83	98	0.73	0.41-1.29	146	185	0.79	0.54-1.15
≥ 22	79	83	1.05	0.63-1.76	65	71	0.68	0.38-1.22	144	154	0.90	0.62-1.30
Stopped within reference year	21	2	10.49	2.24-49.3	23	3	8.15	2.09-31.7	44	5	8.72	3.23-23.5
Stop 1 y before reference year	7	4	3.34	0.77-14.5	9	3	2.05	0.47-8.95	16	7	2.48	0.90-6.82

Table 7. Multivariate-adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Years since last alcohol consumption												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
Stopped within reference year	21	2	11.70	2.48-55.2	23	3	8.03	2.06-31.4	44	5	9.09	3.36-24.6
1	7	4	3.79	0.86-16.7	9	3	1.99	0.45-8.83	16	7	2.52	0.91-7.00
2-4	11	7	1.43	0.47-4.34	13	10	1.64	0.58-4.64	24	17	1.66	0.80-3.43
5-14	18	14	1.45	0.61-3.46	24	32	0.70	0.33-1.47	42	46	0.99	0.58-1.68
≥ 15	25	48	0.53	0.27-1.02	27	34	0.69	0.33-1.44	52	82	0.64	0.40-1.02
Current drinkers	166	230	0.91	0.57-1.46	233	328	0.62	0.37-1.05	399	558	0.79	0.57-1.10
Duration of drinking												
Nondrinkers	84	83	1.00	-----	52	46	1.00	-----	136	129	1.00	-----
< 10	20	32	0.81	0.40-1.65	16	21	0.72	0.31-1.68	36	53	0.80	0.47-1.36
10 to 39	201	224	1.09	0.68-1.74	230	286	0.80	0.47-1.35	431	510	0.93	0.67-1.30
≥ 40	27	49	0.70	0.35-1.42	82	103	0.59	0.33-1.06	109	152	0.75	0.49-1.13
Intake at age 25 &												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
Current drinkers	186	229	1.01	0.63-1.61	268	334	0.72	0.43-1.21	454	563	0.86	0.62-1.20
Former drinkers	23	40	0.68	0.34-1.38	25	46	0.52	0.25-1.05	48	86	0.68	0.42-1.10
Started after age 25	40	37	0.99	0.52-1.87	36	30	0.92	0.46-1.86	76	67	1.06	0.67-1.67

Table 7. Multivariate-adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Drinks per week, age 25												
Nondrinkers	83	82	1.00	-----	51	46	1.00	-----	134	128	1.00	-----
≤ 0.9	123	153	1.02	0.62-1.65	136	155	0.83	0.49-1.43	259	308	0.93	0.66-1.31
1.0 to 2.9	24	26	0.98	0.47-2.04	46	48	0.69	0.35-1.33	70	74	0.84	0.53-1.33
3.0 to 5.9	18	22	1.21	0.53-2.76	31	59	0.47	0.24-0.92	49	81	0.67	0.41-1.09
≥ 6.0	21	28	0.79	0.36-1.76	55	72	0.74	0.39-1.39	76	100	0.76	0.48-1.20
Former drinkers	23	40	0.68	0.33-1.37	25	46	0.52	0.26-1.05	48	86	0.67	0.41-1.08
Started after age 35	40	37	0.99	0.52-1.88	36	30	0.93	0.46-1.86	76	67	1.05	0.67-1.66
Intake at age 35 †												
Nondrinkers	83	79	1.00	-----	50	45	1.00	-----	133	124	1.00	-----
Current drinkers	188	218	0.98	0.61-1.57	270	315	0.72	0.43-1.20	458	533	0.85	0.61-1.19
Former drinker	24	43	0.65	0.33-1.29	34	49	0.59	0.30-1.16	58	92	0.65	0.41-1.03
Drank at later ages	13	12	0.86	0.34-2.21	13	10	0.90	0.32-2.56	26	22	0.98	0.50-1.92
Current drinkers - no data	9	9	0.88	0.27-2.85	4	7	0.89	0.22-3.57	13	16	0.87	0.36-2.07
Drinks per week, age 35 †												
Nondrinker	83	79	1.00	-----	50	45	1.00	-----	133	124	1.00	-----
≤ 0.9	115	130	1.05	0.64-1.74	121	143	0.73	0.42-1.25	236	273	0.87	0.61-1.24
1.0 to 2.9	28	37	0.73	0.36-1.47	50	50	0.73	0.37-1.41	78	87	0.81	0.52-1.27
3.0 to 5.9	23	23	1.33	0.59-2.99	35	60	0.49	0.25-0.95	58	83	0.72	0.45-1.17
≥ 6.0	22	28	0.82	0.38-1.77	64	62	0.88	0.47-1.66	86	90	0.96	0.61-1.51
Former drinkers	24	43	0.61	0.30-1.23	34	49	0.58	0.29-1.14	58	92	0.64	0.41-1.03
Drank at later ages	13	12	0.88	0.34-2.25	13	10	0.91	0.32-2.58	26	22	0.98	0.50-1.92
Current drinkers - no data	9	9	0.86	0.26-2.82	4	7	0.88	0.22-3.52	13	16	0.87	0.36-2.08

Table 7. Multivariate-adjusted Odds Ratios and 95% Confidence Intervals for Breast Cancer Risk Associated with Alcohol Exposure Variables, Stratified by Ethnicity and Case-Control Status

	Hispanic				non-Hispanic				Total			
	Cases (n=332)	Controls (n=388)	OR	95%CI	Cases (n=380)	Controls (n=456)	OR	95%CI	Cases (n = 712)	Controls (n=844)	OR	95%CI
Intake at age 50 †												
Nondrinkers	59	60	1.00	-----	44	33	1.00	-----	103	93	1.00	-----
Current drinkers	93	102	0.89	0.49-1.63	170	171	0.69	0.38-1.24	263	273	0.83	0.55-1.25
Former drinkers	28	41	0.63	0.29-1.36	42	31	0.97	0.46-2.06	70	72	0.79	0.47-1.33
Drank at later ages	2	4	0.19	0.02-1.97	3	1	3.30	0.29-37.8	5	5	0.56	0.14-2.30
Current drinkers - no data	3	2	1.01	0.11-9.29	2	4	0.62	0.08-4.63	5	6	0.43	0.09-2.01
Drinks per week, age 50 †												
Nondrinkers	59	60	1.00	-----	44	33	1.00	-----	103	93	1.00	-----
≤ 0.5	48	39	1.08	0.51-2.29	51	44	0.89	0.44-1.82	99	83	1.08	66-1.75
0.5 to 0.9	9	21	0.39	0.12-1.25	20	21	0.63	0.25-1.55	29	42	0.62	0.32-1.21
1.0 to 5.9	23	36	0.48	0.22-1.07	49	59	0.52	0.26-1.05	72	95	0.62	0.38-1.02
≥ 6.0	13	6	2.14	0.63-7.26	50	47	0.79	0.38-1.66	63	53	1.07	0.61-1.89
Former drinkers	28	41	0.54	0.24-1.20	42	31	0.97	0.45-2.09	70	72	0.80	0.48-1.35
Drank at later ages	2	4	0.16	0.02-1.64	3	1	3.37	0.29-39.1	5	5	0.56	0.14-2.30
Current drinkers - no data	3	2	1.08	0.11-10.7	2	4	0.22	0.02-2.71	5	6	0.43	0.09-2.02

OR, odds ratios; CI, confidence interval; y, year; g, grams

* Adjusted for age, education, age at menarche, menopausal status, age at first full-term birth, parity, breast feeding, fibrocystic disease, years of oral contraceptive use, usual body mass index, smoking, family history of breast cancer, and physical activity

† Numbers are reduced due to exclusion of subjects who were < 35 y or < 50 y at each time point.

& Current drinkers with no data were combined with drinkers.

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Appendix A-1

"Alcohol Consumption and Breast Cancer Among Hispanic and non-Hispanic White Women in New Mexico"

(Doctoral Dissertation Proposal)

Alcohol Consumption and Breast Cancer Among Hispanic and non-Hispanic White Women in New Mexico

I. SPECIFIC AIMS

The incidence of breast cancer in Hispanic women has been documented to be lower than in non-Hispanic white women residing in the West and Southwest (1, 2). In New Mexico, incidence and mortality rates have increased rapidly among Hispanic women since the late 1950s, especially in the younger age-groups, although prevalence rates for Hispanic women are intermediate to those for American Indians and non-Hispanic white women (1-4). Incidence rates increased by 56% over a 19-year period, and mortality increased by almost 100% over the 30-year period 1958-1987 (3). Incidence rates reported for Hispanic women *vs.* non-Hispanic white women range from 58/100,000 *vs.* 112/100,000 for the time-period 1983 to 1987 in New Mexico (3), to 69.8 *vs.* 115.7 for the time-period 1988 to 1992 for Surveillance, Epidemiology and End Results (SEER) data (5).

The proposed study provides an opportunity to further research on the primary cancer for Hispanic women (6). It is projected that Hispanics will represent the largest ethnic group in the US population by the year 2000, and account for approximately 17% of the total U.S. population by the year 2030 (7). New Mexico has the largest percentage of Hispanics (40%) to total state population in the United States (7), and has a statewide cancer registry, the New Mexico Tumor Registry (NMTR), as a part of the SEER Program of the National Cancer Institute. There are 11 SEER geographic areas covering approximately 14% of the US population. This includes 25% of the Hispanic population. The majority of the Hispanic population in the SEER coverage area resides in Los Angeles (60%), New Mexico (10%), San Francisco and San Jose/Monterey (9%), and Connecticut (4%) (5).

Although breast cancer incidence rates and mortality rates have increased among Hispanic women, the causes of breast cancer in this minority population have not been adequately characterized. There are few data available on breast cancer risk factors for Hispanic women (3, 4, 8-10), and in particular, insufficient understanding of dietary and alcohol practices (11). New Mexican Hispanic women, especially over age 50, are reported to have lower alcohol intake, and are more likely to be non-drinkers than non-Hispanic white women (12). One study has reported that alcohol intake was associated with a nonsignificant increased breast cancer risk for Hispanic women (13). Otherwise, the association of alcohol consumption with breast cancer risk has not been investigated in Hispanic women.

The purpose of this study is to evaluate the primary hypothesis that alcohol consumption is associated with increased breast cancer risk among Hispanic and non-Hispanic white women using data from a population-based case-control study, the 'New Mexico Women's Health Study'. The proposed study will result in publishable work on this association for Hispanic and non-Hispanic white women residing in New Mexico. The primary hypotheses are detailed below.

- H_{1A}: The risk of breast cancer for women who consume alcohol is higher than for those who do not consume alcohol, after adjustment for other dietary and nondietary risk factors.
- H_{1B}: The risk of breast cancer for Hispanic women who consume alcohol is higher than for non-Hispanic white women who consume alcohol, after adjustment for covariates.
- H_{2A}: The risk of hormone receptor-negative breast cancer for women who consume alcohol is higher than for those who do not consume alcohol, after adjustment for covariates.
- H_{2B}: The risk of hormone receptor-negative breast cancer for Hispanic women who consume alcohol is higher than for non-Hispanic white women who consume alcohol, after adjustment for covariates.

In order to investigate these hypotheses the following specific aims will be completed. Additional information on previous work is provided under the 'Background' section.

1. To estimate the risk of breast cancer for women who consume alcohol. The weight of evidence has consistently shown an increased risk of breast cancer with alcohol consumption, defined by both a modest and high intake, among both pre- and postmenopausal women (14-16). Risk has been on the order of a 30% to 70% increase. Alcohol consumption as a main effect will be evaluated in terms of both recent and past intake, in addition to lifetime exposure. All three measures have been reported to increase risk of breast cancer (13, 14, 16, 17), although overall, the evidence suggests that alcohol may be more important as a late-stage promoter for breast cancer risk, suggesting a stronger contribution to risk from recent intake (14, 16, 18). Variable distributions, univariate, and stratified analyses will be conducted prior to the modeling stage. Potential confounders will be included in the fully adjusted model. The dependent variable, independent alcohol-related exposure variables, and potential confounders are discussed under the 'Methods' section.

2. To estimate the risk of breast cancer for Hispanic and non-Hispanic white women for alcohol consumption. Studies have primarily included non-Hispanic white women. Only one study of alcohol consumption and breast cancer risk has included Hispanic ethnicity as a risk factor (13). Results for average lifetime alcohol intake indicated a 24% (0.70-2.19) increase in risk per 13 g/day. This study was limited to postmenopausal women in Los Angeles, and the sample size by ethnicity was not included. The proposed study will determine whether the risk of breast cancer varies by level of alcohol consumption when stratified by ethnicity. Additionally, the ethnic-specific odds ratios will be compared, based on the test for heterogeneity. Logistic regression will be used to further evaluate ethnicity while simultaneously adjusting for the other two matching factors, and for other breast cancer risk factors considered to be pertinent confounders.

3. To estimate the risk of hormone receptor breast cancer for alcohol consumption. Hormone receptor status appears to be related to prognosis and survival, and possibly to etiology (19, 20). It has offered an additional insight into associations of certain risk factors (i.e. alcohol, dietary fat, parity, body mass index) and breast cancer (21-24). Some studies (21-23) have shown an association between alcohol consumption and hormone receptor status, variously defined as a single estrogen receptor (ER) measure, progesterone (PR) measure, and the joint combination of ER/PR status. In the cohort 'Iowa Women's Health Study', an increase in risk for ER-/PR- breast tumors was reported for postmenopausal women for 'ever' use of alcohol (RR=1.37, 95%CI 0.86-2.18) (23). This risk increased for women who were in the highest alcohol intake group, and also on estrogen replacement therapy, or had a family history of breast cancer, or who were obese (22). In contrast, a case-control study of Japanese women, aged 25 years and older, failed to find an association between alcohol consumption and joint hormone receptor status (25). However, alcohol exposure was measured dichotomously as 'ever' *vs.* 'never' use, and only 40% of cases had known receptor status. In this analysis, the dependent variable will be categorized as a polychotomous nominal variable based on hormone receptor type of breast cancer (ER+PR+, ER+PR-, ER-PR+, ER-PR-, ERPR unknown). Analyses will follow the same procedure as noted under specific aim one. The number of categories for the dependent variable will depend on receptor type sample sizes. If there appears to be little difference between the subtypes ER+PR+, ER+PR-, ER-PR+, these categories may be collapsed in order to increase power for testing the hypothesis that risk is specifically increased for ER-PR- status.

4. To estimate the risk of hormone receptor breast cancer for Hispanic and non-Hispanic white women for alcohol consumption. To date, there are no studies investigating the presence of a differential risk for hormone receptor breast cancer subtypes and alcohol consumption by ethnicity. Results, based on the large 'Patient Care Evaluation Studies of Breast Cancer' investigation of women 20 to 79 years of age, showed no difference between Hispanic and non-Hispanic white ethnicity for ER/PR status, when ER+PR+ breast cancer cases were compared with ER+PR-, ER-PR+, or ER-PR- cases (26). However, this was a case-case breast cancer study, and the analysis included only 236 Hispanic women out of a total of 410. Risk estimates for hormone receptor-specific breast cancer associated with alcohol consumption will be calculated and stratified by ethnicity, while adjusting for other covariates. The ethnic-specific odds ratios will be compared, based on the test for heterogeneity.

II. BACKGROUND

Alcohol Consumption

Alcohol consumption is a common exposure. Recent statistics provide figures reporting that 61% of women over the age of 18 are current consumers of alcohol (12 or more drinks per year) (27). Of these women, 39.4% reported their usage as light ($\leq$ 3 drinks/week), 27.4% as moderate (4-13 drinks/week), and 9.1% as heavy (14+ drinks/week). Alcohol, as an important component of dietary intake, is subject to modification more easily than the established reproductive risk factors.

There are more than 50 ecological, case-control, and cohort studies examining the association of alcohol and breast cancer (28). The majority, have reported consistent evidence for a positive association between breast cancer and alcohol intake (29). Case-control studies have provided the strongest evidence for an association between alcohol consumption and breast cancer. Rosenberg (17) gives a succinct review of the studies reported in the literature from 1982 through 1992. Studies were included if there were at least 200 prevalent cases with sufficient data on methodology and participation rates no lower than 60%. These studies primarily focused on recent drinking. A total of 18 studies were reviewed. One showed an inverse association and four reported ORs close to the null (< 1.2), whereas eight of the 13 studies with positive associations reported ORs above the null, but $\leq$ 1.8. The remaining four positive studies reported at least one odds ratio above 1.8 and were hospital-based studies conducted in France (OR=3.5 for > 17 drinks/week), and Italy (OR=2.2 for > 3 drinks/day; OR=2.2 for > 24.35 g/day; OR=2.4 for < 0.5 liters/day) (17). Population-based studies have reported lower estimates than hospital-based studies, ranging from 1.2 to 1.7, but have been hampered by lower participation rates of 60% to 80%. In these studies, stratification was not always made on the basis of menopausal status, an important effect modifier of the association between alcohol consumption and risk of breast cancer. However,

associations were noted with alcohol intake prior to age 30. Estimates for dose-response were inconsistent. Some studies showed an increase for those who consumed as little as one drink per day, while other studies reported an increased risk of breast cancer for those consuming only high levels of alcohol (17).

The eight cohort studies of breast cancer reviewed by Rosenberg ranged in follow-up time from 4 to 30 years, and were conducted in the U.S. At least two suffered from high loss-to-follow-up rates. Results showed the following associations: null - 1; positive - 8. Overall relative risk estimates for studies ranged from 1.2 to 3.3. In the four studies with the majority of cases, the relative risk for breast cancer did not exceed 1.6, and was associated with an intake of at least 15+ g/day of alcohol (17).

The recent studies by Longnecker et al. (15, 16, 30) and Swanson et al. (14) built on the previous investigations, and many of their results are detailed below. The following provides a discussion of results for lifetime alcohol consumption, dose-response, recent *vs.* past alcohol intake, beverage type, the association of alcohol and hormone levels in studies of human female subjects, as well as animal studies.

Longnecker et al.'s meta-analysis of 12 case-control studies reported an odds ratios for breast cancer of 1.4 (95% Confidence Interval (95%CI) 1.0-1.8) for consumption of 24 g/day of alcohol (2 drinks), and based on four cohort studies, a relative risk of 1.7 (95%CI 1.4-2.2) associated with consumption of 24 g/day of alcohol (30). Based on six of the case-control studies, the risk of breast cancer associated with 'ever' alcohol consumption was increased by only 10% (OR=1.1, 95%CI 1.0, 1.2). This attenuation is probably due to the fact that the majority of women were light to moderate drinkers and the inherent limitations present in the case-control design (30). In their case-control study, based on 15,825 subjects from four states, Longnecker et al. (16) ascertained pre- and postmenopausal incident breast cancer cases < 75 years of age who were diagnosed from 1988 through 1991, and reported to statewide cancer registries. A telephone questionnaire was used to assess alcohol intake of beer, wine, and liquor during five periods of life (16-19, 20-29, 30-39, 40-59, 60-74 years). Controls were drawn from two different sources and frequency-matched by age group. Average lifetime alcohol consumption was based on the period from 16 years of age through the previous age interval. Lifetime average consumption for 13 g/day compared with lifelong abstainers was associated with a 31% increase in risk of breast cancer (95%CI 1.20-1.43), and a statistically significant trend across categories of alcohol consumption.

The recently reported case-control study by Swanson et al. (14), was based on 1,645 premenopausal incident breast cancer cases diagnosed during 1990-1992 in women 20 to 44 years of age, and frequency-matched to controls. The odds ratio for women defined as ever drinkers compared to nondrinkers was 1.1, (95%CI 1.0-1.3). A primary focus of this study was the effect of recent *vs.* usual alcohol intake by level of consumption, since previous studies had noted indirect evidence for the importance of recent alcohol intake. They evaluated alcohol usage patterns, exposure periods reflecting the teens, twenties, and thirties, beverage type, and stage of disease.

The strongest evidence for a dose-response relationship of alcohol consumption and the risk of breast cancer comes from Longnecker et al.'s 1995 large, case-control study (16). Risk of breast cancer showed a monotonic increase by alcohol intake for all subjects combined with the exception of the highest category of alcohol intake (OR=1.75, 95% CI 1.16-2.64 for 46+ g/day alcohol). Results ranged from an odds ratio of 1.13 (95% CI 1.01-1.26) for 0-5 g/day alcohol, to 2.30 (95% CI 1.51-3.51) for 33-45 g/day alcohol (16). The risk estimate based on a continuous measure of the lifetime average number of grams of alcohol consumed daily was 1.31 (95% CI 1.20-1.43, P for trend <.0001) for 13 g/day (1 drink). Swanson et al. (14), found an increased risk for breast cancer at a high dose (14+ drinks/wk) (OR=1.7, 95%CI 1.2-2.5), but no clear dose-response or gradient across categories of alcohol intake. Howe et al.'s study suggested a possible 'threshold' effect based on a pooled analysis of six case-control studies (31). A significant increase in risk was seen for women consuming 40 g/day or more of alcohol (OR=1.6 (95%CI 1.19-2.40), adjusted for total energy, fat, fiber, and vitamin C. The possibility of a threshold effect would require levels of alcohol intake to be high in order to detect an association.

Longnecker et al.(16) and Swanson et al.'s (14) investigations have shown a stronger association between 'recent' alcohol consumption and increased risk of breast cancer when stratified on time-period for alcohol consumption. In Longnecker et al.'s case-control study, 'recent' alcohol consumption was defined as intake in the previous age interval prior to the reference date, and 'past' alcohol consumption as intake prior to 30 years of age. Results indicated that 'recent' *vs.* 'past' alcohol consumption appeared to be more strongly associated with risk of breast cancer (OR=1.21 for 13 g/day alcohol, 95%CI 1.09-1.34 *vs.* OR=1.09 for 13 g/day alcohol, 95%CI 0.95-1.24). Swanson et al. reported a 70% increase in risk of breast cancer associated with 'recent' alcohol consumption (OR=1.70, 95%CI 1.2-2.5), although this was restricted to women consuming $\geq$ 14 drinks /week (14). The risk in the latter study increased to 2.4 (95%CI 1.6-3.8) when stratification was further restricted to women with a regional/distant diagnosis suggesting the importance of disease stage. Past alcohol consumption was based on the average intake for women during their teens, twenties, and thirties (14). Results by level of alcohol intake for the three age-period exposures indicated that risk increased 34% (95%CI 0.7,

2.6) in the teen years for consumption of ≥ 7 drinks per week, 29% (95%CI 0.9, 2.0) in the twenties for consumption of ≥ 14 drinks per week, and 80% (95%CI 1.2, 2.6) in the thirties for consumption of ≥ 14 drinks per week.

The pattern of risk by beverage consumption (wine, beer, hard liquor) has not always been consistent, and studies have varied as to which beverage, if any, carries the highest risk (32). This issue is a hard one to disentangle due to the mixture of beverages that tends to occur with alcohol consumption. Swanson et al.'s (14) study reported the strongest risk for beer consumption (OR=2.6, 95%CI=1.4-4.8) compared to wine and liquor intake; whereas Longnecker et al.'s (16) study showed an increased risk for both beer (OR=1.25, 95%CI=1.13-1.39) and liquor (OR=1.18, 95%CI=1.07-1.31). Mutual adjustment for beverage type in the study by van den Brandt et al. (29) suggested that the association was present for wine (OR=1.50, 95%CI 0.63-3.57), and liquor (OR=1.67, 95%CI 0.82-3.39), but not for beer consumption (OR=0.95, 95%CI 0.61-1.48). However, associations reported for one beverage *vs.* another may merely reflect the dominant beverage consumed by the heaviest drinkers. Although some studies have shown a difference in risk by beverage type, risk has not been consistently associated with one type, implying that risk is associated with alcohol intake in general, and not with any other specific component.

There is no definitive evidence for a causal mechanism associating alcohol consumption with breast cancer risk. However, a small clinical trial has proposed a possible mechanism for the positive association between alcohol consumption and breast cancer, with the detection of a statistically significant increase in plasma and urinary hormones. A group of 34 premenopausal women, aged 20-40 years, was enrolled in a controlled-diet study for six consecutive months. Subjects served as their own controls to reduce interindividual variation. Following exposure to 30 g/day of ethanol for three menstrual cycles, they abstained from alcohol for the remaining three cycles. Results showed elevated serum levels of total and bioavailable estrogen (33). An increase in plasma estradiol levels has been shown to also increase three-fold in postmenopausal women following a single dose of 0.7 g/kg alcohol (34).

The link of alcohol with estrogen level provides a rational mechanism between alcohol intake and breast cancer, implying an effect on estrogen production and metabolism. Estrogen and progesterone are required for the cyclic proliferation of mammary ductal cells during the menstrual cycle and for lobuloalveolar growth during pregnancy. Hormonal level is hypothesized to be important in the etiology of breast cancer by increasing breast epithelial cell division during relevant developmental periods, and enhancing the possibility of carcinogenesis (35). Studies in the 1970s established increased plasma estrogen and estradiol levels in postmenopausal women with breast cancer (36), supporting the hypothesis that breast neoplasia is the result of excessive hormonal stimulation. Many established risk factors act as contributors to a cumulative index of estrogen and progesterone exposure (early menarche, late menopause, obesity in postmenopausal women, and hormone replacement therapy) (37), and should be adjusted for in analysis.

Results based on experimental animal models of alcohol exposure and breast cancer are inconsistent (38-40). These studies are difficult to conduct, because there are few good animal models of spontaneous breast cancer. Most studies are conducted using rodents; dogs, although they develop natural spontaneous breast tumors, are considered too expensive for most studies (38). Most studies report no association between alcohol and mammary carcinogenesis (39). McDermott et al. (39) conducted an experiment in which female Sprague-Dawley rats given an established carcinogen were randomly assigned to dietary ethanol (4.4g/kg/day) or placebo. The incidence of tumors was significantly lower in the ethanol than control group ($p < 0.001$), and there was no statistically significant difference between groups in mean number of tumors, tumor growth rate, or time of appearance of first tumor. Endocrine levels were not measured for the two groups. Positive results have shown that ethanol consumption > 20% of calories decreased serum progesterone and mammary gland maturation and differentiation resulting in an increase in the density of carcinogen sensitive histological structures (41, 42). These changes might increase susceptibility to breast cancer carcinogens, but would not necessarily cause cancer. It has been suggested that progesterone when co-occurring with estrogen may further increase mitotic activity in breast epithelium (37).

Reasons cited for the inconsistent or negative results from animal studies include mode of ethanol administration (gavage, drinking water, liquid diet), and amount of ethanol administered which has usually been 20% or more of total calories with no evaluation of lower doses (40). These factors are thought to have an effect on the rate of ethanol absorption, level and duration of ethanol, and blood-level metabolites, all of which might subsequently affect metabolism (40). Ethanol administered as part of a natural product diet *vs.* a liquid diet may also result in in tumor response variation (40).

In summary, a majority of both case-control and cohort studies indicate an increased prevalence of alcohol intake in cases, an increased incidence of breast cancer in those drinking > 14 g/day, an increased risk associated with dose, as well as risk differential associated with timing of exposure (recent *vs.* past alcohol intake). In general, risk appears to be associated with alcohol consumption regardless of beverage type, suggesting that ethanol is the actual risk factor. Although the weight of experimental animal studies does not tend to support the alcohol-breast cancer risk hypothesis, small human clinical studies have suggested that alcohol exerts an effect on breast cancer risk by increasing

estrogen levels. These changes might increase susceptibility to breast cancer carcinogens by acting as promoters. Although the scanty results from animal experiments have been inconsistent for breast tumorigenesis, alcohol is still an established carcinogen for other cancer sites and its effect on serum hormone levels has been identified (18). By analogy, the pattern for the association between breast cancer and alcohol, as well as other known or considered risk factors, does not appear dissimilar. Certainly, the risk associated with several of the reproductive factors (early age at menarche, late age at menopause, absence or short duration of breastfeeding) is within the 1.5 to 2.0 range, which covers the estimate generally reported for alcohol and breast cancer (43). Although not all studies were conducted with an '*a priori*' hypothesis, and the effect is modest, there is a consistency in the trend and magnitude of the well-designed large studies (44).

Hormone Receptor Status of Breast Tumors

Hormone receptor status has received attention as a means of identifying subtypes of breast cancer that are not only related to prognosis and survival, but possibly to separate risk factors for breast cancer (19, 20). Estrogen receptor protein binds and transfers estrogen to the nucleus of a cell, and is found in about 60% of breast cancers (45). The number of estrogen receptors in breast cancer cells is associated with cell differentiation, with tumor response to antiestrogen or tamoxifen therapy, and to oophorectomy (46). Receptor-positive tumors are reported to occur more frequently among postmenopausal women than among premenopausal women (45). Patients with both ER+/PR+ status are characterized by the highest response rates (approximately 70%) to endocrine therapy, whereas those with ER-/PR- tumors (approximately 10%) show the poorest response, and those with discordant status (30-40%) show an intermediate response (47 249, 48)

Several studies have demonstrated an association of alcohol consumption with hormone receptor status, although analyses and results have varied by use of separate subtypes, ER or PR status, (21), or the joint combination of ER/PR status (22, 23). Risk factors for breast cancer, including family history of breast cancer (49), body mass index (BMI) (50), dietary fat (24, 51), parity, age at first birth, age at menarche, BMI, and body fat distribution (23) have shown different patterns by hormone receptor status. These results may suggest different etiologies associated with disease heterogeneity or separate hormone receptor subtypes. Based on data from a case-control study conducted in New York (1982-1984) of 1,152 women, aged 20-79 years of age, Nasca et al. reported an odds ratio of 1.18 (95%CI 0.88-1.57) for <1.5 g/day alcohol with an increase to 1.35 (95%CI 0.99-1.85) for ≥15.0 g/day alcohol associated with ER+ breast tumors (21). Breast cancer cases with ER+ status were more likely to be ≥ 65 years (64%) compared to ER- cases (54%), to have reported the cessation of menstruation (77% *vs.* 68%), and to have a greater duration (14+ years) of cigarette smoking (37% *vs.* 30%), following adjustment for covariates.

Data from the cohort, 'Iowa Women's Health Study', based on 610 (65%) women with a joint ER/PR status out of 939 women identified with incident breast cancer and aged 55-69 years, showed an association between PR+ status and risk factors which measure endogenous hormone exposure (23). However, alcohol use within the last year was found to increase the risk for ER-/PR- breast tumors in both stratified (RR=1.55 (95% CI 1.00-2.41), and polychotomous logistic regression analyses (RR=1.37 (95% CI 0.86-2.18). Gapstur et al. (22) extended analyses of the 'Iowa Women's Health Study' to evaluate the risk of breast cancer hormone receptor status and the presence of interaction between alcohol consumption (0, < 4.0, ≥ 4.0 g/day) with three other risk factors. ER-/PR+ was excluded due to small sample size. Relative risks by hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR-) for those on estrogen replacement therapy were reported to be 1.8 (95%CI 1.3-2.5), 1.3 (95%CI 0.6-2.5), and 2.6 (95%CI 1.4-4.9) respectively, at the highest alcohol intake of ≥ 4.0 g/day. Results for family history were 1.7 (95%CI 1.2-2.5), 0.8 (95%CI 0.3-2.3), and 3.1 (95%CI 1.6-6.2) for women with any level of alcohol intake, and results for the highest quintile of BMI > 30.70 were 0.9 (95%CI 0.5-1.9), 1.8 (95%CI 0.7-4.7), and 2.0 (95%CI 0.7-5.6) for 'drinkers' (22)

In contrast to these results, the initial analyses of the association between alcohol consumption and breast cancer for the 'Iowa Women's Health Study' showed only an age-adjusted relative risk of 1.28 (95% CI 0.93-1.76). This risk increased (RR = 1.46, 95% CI 1.04-2.04; P for trend=0.04, for the highest alcohol intake of 15+ g/day) with adjustment for covariates (BMI, age at first livebirth, age at menarche, and family history of breast cancer) (52). Significant multiplicative interaction was detected between alcohol intake and noncontraceptive estrogen use for the two highest levels of alcohol intake (RR=1.88, 95% CI 1.30-2.72 for 5.0-14.9 g/day; RR=1.83, 95% CI 1.18-2.85 for 15+ g/day), whereas there was no association between alcohol and breast cancer detected among never-users of estrogen (52).

The association of ethnicity with hormone receptor status was examined for 13,239 breast cancer cases in the 'Patient Care Evaluation Study of Breast Cancer', ascertained during 1990 (26). The status group ER+/PR+ was used as the referent group in the polychotomous logistic regression analysis which did not show a significant difference for ERPR status for Hispanic *vs.* non-Hispanic white women: ER+PR-, OR=0.88 (95% CI 0.65, 1.21); ER-PR+, OR=1.20 (95%.CI 0.83, 1.75; and ER-PR-, OR=0.95 (95% CI 0.74, 1.23). However, this may be due to the lack of a true nondiseased control group.

Studies of Hispanic Ethnicity and Breast Cancer Risk

Studies have shown that incidence and mortality rates for other chronic diseases such as diabetes and heart disease also show a different pattern for Hispanics compared with non-Hispanic whites in New Mexico (53). The Hispanics residing in New Mexico are primarily lifelong residents (75%), compared to only 15% of non-Hispanic white women. Additionally, for many, their families have lived here for several generations, and are composed of descendants of Spanish colonists of the 16th, 17th, and 18th centuries who intermarried with Pueblo Indians and recent Mexican immigrants. Thus, they are not strictly comparable to other Hispanic groups such as Mexican-Americans who are recent migrants to the United States. However, the Hispanic population in the U.S. is characterized by a diversity across a spectrum of factors, including background nationality, ethnicity, socioeconomic status, social class, culture, and religion (7).

As noted previously, there are few published studies comparing Hispanic women with other ethnic groups for breast cancer. Two studies conducted in Texas reported a lower incidence of familial breast cancer among Hispanic women compared to Blacks and non-Hispanic whites (8), and the suggestion of an increased risk of mortality due to breast cancer with increased age at first child-birth (4). Hispanic women, over the period 1980 to 1992, were reported to have more Stage IIA breast cancer than non-Hispanic white women (37% *vs.* 28%), and to be less than 50 years old at age of diagnosis (44% *vs.* 28%) (54). In contrast, based on SEER data, Hispanic women were reported to present at an earlier stage of diagnosis for the time-period 1983-1992 compared to 1973-1982. However, although detection now occurs more frequently at the local stage, survival has not improved (55). In an analysis of the 148 Hispanic cases and 167 controls (43% based on New Mexico Hispanics), drawn from 'The Cancer and Steroid Hormone Study (CASH)', a statistically significant increased risk for breast cancer was found for women who reported having a mother or sister with a history of breast cancer (OR=1.89) (9). Although not statistically significant, the expected pattern for number of full-term pregnancies, age at first full-term birth, and benign breast disease were found, but not for early age at menarche.

Latino ethnicity was found to be a significant predictor of dietary and alcohol intake after adjustment for relevant covariates in a study of California Latino dietary practices (11). Latinos compared to non-Latino whites were less likely to have had liquor in the past month (OR=0.6). Less acculturated (greater use of Spanish language) Latinos compared with highly acculturated (greater use of English) Latinos reported less alcohol consumption in the past month (OR=0.7). Post-menopausal Hispanic women in New Mexico, compared to non-Hispanic whites, are reported to have a similar intake of beer, but less intake for wine and liquor (56) and overall, alcohol consumption is lower.

In a study of 6,678 breast tumor specimens, Elledge et al. reported that Hispanic women had worse overall 5-year survival compared to non-Hispanic white women (65% *vs.* 75%), and differed for tumor biologic factors (57). Significant differences, based on the Hispanic *vs.* non-Hispanic white comparison, were present for age (61% *vs.* 76%), tumor size (32% *vs.* 45%), and nodal status (30% *vs.* 21%). Age was found to modify the association between ethnicity and hormone receptor status. Hispanic women were intermediate to non-Hispanic whites and Blacks for ER+ status tumors for ages 35 to 50 years, (P for difference < 0.12), and for 50 years or greater (P for difference <.002). This was also true for PR+ status for women 50 years of age or older (P for difference < 0.006) (57). Further investigation into the association of Hispanic ethnicity with ER status may be of significance given that survival rates have been reported to be lower in patients with ER- tumors compared to patients with ER+ tumors, although this may have more to do with pre- *vs* . postmenopausal status, since it also has been reported that postmenopausal patients are more frequently reported to have receptor-positive tumors (45).

III. METHODS

The data for the proposed study is drawn from the 'New Mexico Women's Health Study' (NMWHS), a statewide population-based case-control study of breast cancer in Hispanic and non-Hispanic white women. Women newly diagnosed with an invasive or *in situ* breast carcinoma during the period January 1, 1992 through December 31, 1994, who were residents of the state, and 30 through 74 years of age at diagnosis were eligible for the study.

Selection Of Case Subjects

All eligible Hispanic cases were included. Hispanic ethnicity was based on Spanish surname identified by means of a computer program based on the 1980 Census Bureau list of Spanish surnames, and a computer program (GUESS) that evaluates beginnings, endings and specific letter combinations in a last name (58). The overall expected number of breast cancer cases for the study period was approximately three times higher for non-Hispanic cases compared with Hispanics. A random sample of approximately 33% of non-Hispanic white cases based on age group (30-39, 40-64, 65-74 years) and geographic region, defined by seven state health planning districts, was identified for inclusion. The sampling fraction for non-Hispanic whites in each of these 21 strata was chosen to give a distribution similar to the age and geographic distribution of Hispanic cases ascertained by the NMTR in the three-year period 1988 through 1990. There was a total of 486 eligible breast cancer Hispanic cases. Random selection of non-Hispanic whites

resulted in 505 cases. Of these, 991 eligible cases, 331 Hispanic (68.1%) and 380 non-Hispanic white women (75.2%) completed interviews. These response rates are lower than for controls (see below), and for the in-person interview study of alcohol consumption reported by Swanson (86%) (14), and the telephone-based interview reported by Longnecker (80%) (16). However, state-specific response rates in Longnecker et al.'s study ranged from 74% for Maine to 86% in New Hampshire among four states. These studies were based primarily on non-Hispanic white subjects.

Selection Of Control Subjects

Controls were frequency-matched on the basis of Hispanic and non-Hispanic white ethnicity, three age groups (30-39, 40-64, 65-74), and seven health planning districts. Controls were ascertained through a modified approach to the Waksberg random digit dialing method (59). Data from the NMTR collected over the past 26 years were used to build a pool of prefixes known to contain residential numbers for control selection. This pool was based on those prefixes which had contributed at least one breast cancer case to the NMTR database. This restricted pool of prefixes was used to increase the likelihood of generating a larger pool of 'working' residential phone numbers; a real concern due to the sparsely populated counties of New Mexico. Additionally, a random sample of phone numbers linked to gender, health planning district, ethnicity, and age-group were used to efficiently locate and recruit a sufficient number of older, rural Hispanic controls due to the difficulty in ascertaining this subset of women.

A total of 8,147 working telephone numbers were contacted; of these, 4,459 were residential numbers. There were a total of 1,039 eligible controls ascertained from 3,400 respondents who completed the telephone screening interview; 511 Hispanic and 528 non-Hispanic white women. Of these, 388 (75.9%) Hispanic, and 456 (86.4%) non-Hispanic white women completed interviews. Overall response rates for controls stratified by ethnicity could not be calculated because ethnicity of non-respondents was unknown. However, the response rate for Hispanic control subjects is comparable to that for Swanson et al.'s study (78.7%) (14), and the response for non-Hispanic white controls is similar to the rate reported by Longnecker et al. (84%) which ranged from 79% in Massachusetts to 90% in Wisconsin (16).

Data Collection

The University of New Mexico's Human Research and Review Committee approved the NMWHS project. Physician consent was obtained for all cases and a written informed consent was signed at the onset of the interview. Interviews were conducted in-person at a subject's home or an agreed upon location and averaged two hours. The two primary questionnaires, the 'Food Frequency Questionnaire (FFQ)' and the'Risk Factor Questionnaire (RFQ)', are included in the Appendix.

All questionnaires were translated into Spanish and interviews were conducted in Spanish or English by bilingual interviewers according to the participant's preference. The RFQ included questions on demographic characteristics, education, income, ethnic identification and acculturation factors, and primary breast cancer risk factors related to reproductive and menstrual history, use of oral contraceptive and exogenous hormones, family history of breast disease, personal history of breast disease, radiation, weight (at 18 years and current), height, current physical activity, as well as cigarette smoking, and history of alcohol consumption. To aid respondent recall, interviewers used a calendar that recorded their major life events. Only events that occurred before each woman's reference date were recorded (date of diagnosis for cases, date of interview for controls). Ethnicity will be based on the subject's self-report at the time of interview. Subjects who reported Hispanic or non-Hispanic white ethnicity will be included in the proposed study. Interviewers were not informed as to case-control status, and the alcohol and dietary data for the FFQ was collected at the beginning of the interview.

Recent dietary intake, including alcohol consumption based on intake of wine, beer, and hard liquor, was collected using a semiquantative food frequency questionnaire. The FFQ was designed by staff of the Human Nutrition Center at the University of Texas, Houston School of Public Health, and was a modified version of one used in a Texas Hispanic population (60). Modifications were made by Dr. R. Sue McPherson to add foods to the FFQ that were important sources of nutrients among New Mexico women. Following an analysis of food intake recalls of 100 women, based on local food sources of energy, macronutrients and vitamins were added to the FFQ resulting in a 140 item questionnaire. Standard protocols for the development of the FFQ were used (61, 62). Emphasis was placed on adding specific foods, rather than grouped foods, because recall is considered to be better for specific items (63, 64). Frequency of use information included consumption on a per month, week, or day basis, and was averaged over a 28-day month for an estimated daily intake. Two-dimensional food models were used to aid in the determination of portion size which included data on number of servings, the type of food model, and thickness of food as appropriate. Frequency of consumption and portion size data were entered into the 'Food Frequency Data Entry and Analysis Program' which contained the gram weight and nutrient data to calculate nutrient estimates per food per day (65). In an effort to avoid the potential impact of disease or treatment, all subjects were asked to recall 'usual' food intake for a four-week period six months prior to the interview. If a subject reported that their diet was not 'usual' during this time, due to any reason, they were asked to recall the months prior to any major impact on 'usual' food intake.

Independent Variables

Alcohol consumption will be studied in terms of recent intake and past history. Recent alcohol intake expressed in grams per day will be categorized based on the FFQ. Average daily alcohol consumption is based on the summation of the three beverage types. Alcohol abstinence will be based on those women reporting an intake of 0 grams per day. The distribution of these data will be evaluated for skewness and will be transformed, if necessary.

Questions in the RFQ related to alcohol intake included ever *vs.* never use, age at first use, and age at cessation. History of past exposure included questions for alcohol intake at age 25, 35 and 50 years, as appropriate. Lifetime alcohol consumption will be estimated as the average intake for the previous age points 25, 35, and 50 years. The frequency of use, and the number of drinks per week by beverage type were recorded. Frequency of use included: 4 or more times per day; 2-3 times per day; once per day; 2-3 times per week; once per week; once per month; 2-3 times per month; 2-3 times per year; and never. The ethanol content for each type of beverage will be based on the standard amounts: 12.8 g/alcohol for one serving of beer; 10.9 g/alcohol for one 4-ounce glass of wine; 15.0 g/alcohol for one hard liquor drink (66). Alcohol consumption will be categorized similarly to Longnecker et al.'s classification which correlated the median alcohol intake within the higher categories to one drink of alcohol (12-18 g alcohol), two drinks (19-32 g alcohol), three drinks (33-45 g alcohol), and four or more drinks ($\geq$ 46 g alcohol) (16).

Alcohol consumption also will be analyzed as a continuous variable, per 13 grams of alcohol per day (1 drink), as a comparison with results based on Longnecker et al.'s case-control study (16). Models of the square root of alcohol consumption were found to fit the data better than untransformed alcohol intake, and produced similar risk estimates to the categorical analysis (16).

Dependent Variable

Breast cancer diagnosis for this study includes all incident invasive or *in situ* breast carcinomas. In order to address hypotheses 2A and 2B, breast cancer will be categorized on the basis of hormone receptor subtypes. Hormone receptor assays were conducted in laboratories associated with the hospitals where cases were diagnosed. The status of hormone receptors as noted in the medical records of subjects was collected by the SEER abstractors; specific receptor activity values were not recorded (67). Breast cancer will be categorized by the joint classification of ER/PR status (ER+PR+, ER+PR-, ER-PR+, ER-PR-, unknown). If either ER or PR status is unknown, the joint status will be considered 'unknown'. It is possible that the distribution for more than one of the categories will have a very small sample size and be dropped from analysis. Preliminary data regarding separate receptor status categories indicate that approximately 52%, 24%, and 24% are recorded as ER+, ER-, and missing for ER status, respectively (68). There are approximately 44%, 31%, and 25% characterized by PR+, PR-, and missing for PR status (68). The prevalence rates for ER+ and PR+, and the number unknown, compare favorably with those reported by Gapstur et al. (22), in which the prevalence of ER+, ER-, and ER missing was 59%, 11%, and 30%, and the prevalence for PR+, PR-, and PR missing was 46%, 19%, and 35%. In Nasca et al.'s study on ER receptor status and alcohol consumption, 25% of subjects had missing data (21).

Confounding Variables

Breast cancer, like most cancers, is multifactorial and to date it is difficult to attribute more importance to one cause over another. Relevant covariates will be evaluated in estimating the main effect for alcohol consumption. In addition to the matching factors of age-group and district, variables considered as confounders will be included in ethnic-specific analyses for purposes of adjustment. In general, previous studies have categorized these variables. Category boundaries for variables that are not dichotomous (benign breast disease, family history of breast cancer) will be evaluated on the basis of the most commonly accepted cutpoints (ie. menarche, < 12 *vs.* ≥ 12 years; age at first livebirth, < 30 *vs.* ≥ 30 years), and on the basis of the quantile distribution. However, categorization of data will be evaluated for all variables to determine whether final groupings are too broad to detect does-response changes or too narrow to provide stable estimates (69). Continuous variables will be evaluated to determine the scale that best approximates the dose-response based on the categorical form, and to determine whether to use the variables in a continuous or categorical form. Variables found to have no effect on the results may not be included in the final, fully adjusted model (e.g. total fat, total energy).

The variables to be included in analyses where breast cancer is treated as a dichotomous outcome are based on several previous studies and include: education, age at menarche, age at first full-term pregnancy, parity, age at menopause, menopausal status, benign breast disease, family history of breast cancer, current BMI (weight (kg)/height $(m)^2$) calculated from the self-reported height and weight, BMI at age 18 calculated from height and weight at age 18, estrogen replacement therapy, contraceptive estrogen use, total caloric intake, and total fat intake (13, 14, 16, 30, 32, 52, 70, 71). Analyses based on breast cancer as a polychotomous nominal outcome (hormone receptor-specific subtypes) will include these same covariates (21-24).

Methods of Data Analysis

Data analysis will be performed using STATA (72), SAS (73), and JMP (74). Descriptive statistics will be calculated for all variables included in the analysis, and will be evaluated for errors, missing data, outliers, and small samples for categories of exposure. These summaries, including contingency tables, scatterplots, and histograms will be conducted for all subjects combined and stratified by ethnicity. Stratified analyses will be used to investigate the distributions of the confounders and the presence of stratum-specific differences or effect-modification.

Univariate analyses (ORs and 95 percent confidence intervals) (75) will be stratified by ethnicity for each risk factor to compare the risk estimates of Hispanic and non-Hispanic white women. Stratum-specific analyses will be used to investigate the relationship between alcohol-intake variables and the other covariates when sample size permits. Odds ratios will be estimated using multivariate conditional logistic regression to simultaneously adjust for the confounders previously noted, and any possible interaction, while allowing for the matching factors of age-group and district (76). These analyses also will be stratified by ethnicity.

The model building strategy suggested by Hosmer and Lemeshow (76) will be used to guide analyses for the development of a final, fully adjusted model. Estimated coefficients from the multivariate models will be compared with those from the univariate models using the Wald statistic as a guideline for model reduction. The likelihood ratio test will be used to compare models to detect the presence of confounding and the need for adjustment. At the final model stage, a check for the scale of any continuous variables will be made. The fit of the model will be determined by using the Hosmer-Lemeshow goodness-of-fit statistic which evaluates a model on the basis of the χ^2 distribution (76). Test of trend will be calculated for any variables used in continuous form and based on two-sided tests. An energy adjustment method will be used to remove extraneous variation from the correlation of total fat and alcohol with total energy intake to reduce measurement error, and to control for confounding by energy intake (63).

In addition to menopausal status, alcohol has been reported to interact with estrogen replacement therapy, BMI, and family history of breast cancer (22, 52, 70, 71). Effect modification will be assessed by including product terms in the final model, if warranted, based on stratum-specific effects if there is sufficient sample size. The presence of interaction, if present, will be assessed using $p < 0.05$, and a statistical assessment for relevant contribution to the model made by using the likelihood ratio test. The ability to detect the presence of effect modification will be limited by the sample size, especially so for the highest levels of alcohol intake. Overall, the magnitude of the alcohol-breast cancer association has not been reported to be greatly reduced subsequent to adjustment of these covariates (77).

Sample Size and Statistical Power

The original grant application for the NMWHS included power calculations and minimum detectable risks for all subjects combined and by ethnic group (Hispanic, non-Hispanic white). Dietary nutrient intake, including alcohol consumption, was based on quartiles. The calculations demonstrated adequate power for main effects within the two ethnic groups (68), although the final study sample size by ethnicity (Hispanic: 331; non-Hispanic white: 380) did not equal the projected number of 400 Hispanic and 400 non-Hispanic white women. An estimate for 'recent' alcohol intake for all subjects based on preliminary data from the FFQ yielded a minimum detectable risk of 1.33 (power=0.80, significance level of 0.05, two-sided test, 1:1 matching ratio). This estimate is based on a prevalence of 47% (positive response to any alcohol intake), 713 cases, and 827 controls (68). The estimate for 'past' alcohol intake, based on the RFQ, yielded a minimum detectable risk of 1.59 for all subjects and 1.85 for Hispanics *vs.* 2.22 for non-Hispanic white using the same parameters noted above. These estimates were based on an overall prevalence of 87% (positive response to 'ever' alcohol intake); 83% for Hispanic women and 91% for non-Hispanic white women (68).

Limitations and Strength of the Case-Control Design

As always, selection, information, and confounding biases must be considered in evaluating results from case-control studies. Nonresponse rates have most certainly varied by study, but for Longnecker et al.'s landmark study of alcohol and breast cancer, participation was greater than 80% for both cases and controls. This is compatible with rates reported for two large prospective studies, 84% and 89% (52, 71), reducing the concern over selection bias. The proposed study based on a population-based case-control design is not subject to many of the limitations imposed by the use of referral centers or the use of hospital drawn controls. However, response rates, particularly for Hispanic cases, are low and may reflect the possibility of bias. Although a comparison can be made between case nonrespondents and participants on a number of variables such as age, stage of disease, and year of diagnosis, there is no information available for a comparison of risk factors collected via the questionnaires. Additionally, issues of selection bias cannot be directly assessed in relation to control nonrespondents.

Case-control studies are particularly susceptible to recall bias. In general, the assessment of alcohol intake suffers from the same measurement error problems associated with nutritional intake; however, food frequency questionnaires have been extensively evaluated and found to be both valid and reliable for ranking individuals' usual

nutrient intake (78, 79). Fortunately, several studies focusing on this limitation have reported reliability results that are acceptable for report of alcohol consumption (71, 80-83). Willett et al. studied the effects of recall bias on reported alcohol consumption in the Nurse's Health Study (71). There was little evidence for more than a modest effect; the odds ratio for the retrospective assessment was only slightly reduced (OR = 1.42), compared to that for the prospective assessment (OR = 1.55). A later reliability analysis of this cohort study yielded a correlation of 0.84 between current intake and past intake from four years in the past (81). The reliability of self-reported alcohol consumption appears to be sufficiently precise to rank subjects consistently within the same drinking category for recent consumption (6 to 12 months) of alcohol (Spearman correlation coefficient = 0.77), the timeframe that appears to be the most relevant in alcohol-breast cancer research (18, 82). Cohort (NHANES) evaluation for recalled alcohol intake from 10 years in the past yielded a Spearman correlation coefficient of 0.68 for women in general (83). Heavy drinkers (>10 drinks/week) significantly underestimated their intake (Kappa = 0.45, $p < .05$), and older women (e.g. 44-46 years, Spearman correlation coefficient = 0.74) tended to be more reliable than younger women (e.g. 24-26 years, Spearman correlation coefficient = 0.57) (83). Issues related to recall bias should have no impact on hormone receptor status; however, this analysis may suffer from measurement error since results are from many different institutions. However, it has been noted that the categorization of tumors as hormone positive or negative is reliable (19).

There are a number of confounding variables to be evaluated in the multivariate analyses, and the comparison of models will guide the inclusion of confounders in the final adjusted model. There is always the possibility of additional, unknown confounding exposures that should be adjusted for, but at this time, it appears that sufficient data is present to adjust for those factors considered to be relevant based on previous studies. In the many analyses conducted, there are a number of variables and possible interaction terms to be examined, introducing the possibility of multiple comparisons. Interaction terms will be entered into models and tested as part of a group to reduce the number of comparisons evaluated. This issue, along with the biases noted above, and sensitivity-specificity issues regarding case and control ascertainment and response, will be discussed in the manuscript.

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Appendix A-2

- Statement of Work
  (from USAMRMC original 'Predoctoral Fellowship Application')
- Timeline
  (from USAMRMC original 'Predoctoral Fellowship Application')

Part 1. D. STATEMENT OF WORK

It is neither possible nor desirable to produce a structured statement of tasks to be accomplished during defined time periods for the proposed coursework and dissertation research, since progress is controlled to a large extent by the faculty and administration of the supporting educational institution. The time-line shown on the next page has been provided as a general guide, rather than a structured statement of work.

The time-line essentially divides the 3 year fellowship request into four critical time-blocks in which specific objectives are to be met.

Time-Block 1: This block represents the required year of coursework for qualification for the doctoral degree at the University of Texas School of Public Health. A minimum of 36 hours of coursework are required before approval to take the doctoral qualifying examination. The following is a tentative list of courses available at UTSPH that may be taken.

Proposed Coursework: University of Texas School of Public Health (UTSPH) Courses by Call Number (see 1993-1995 Catalog)

1996 (12 courses, 36 credit hours minimum required prior to Doctoral Qualifying Examination)

PH 1820 Applied Statistical Analysis I
PH 1821 Applied Statistical Analysis II
PH 1830 Advanced Statistical Methods in Epidemiology
PH 1831 Analysis of Survival Time Data
PH 2165 Mutagenesis and Carcinogenesis
PH 2175 Principles of Toxicology
PH 2712 Advanced Epidemiologic Methods III
PH 6215 Nutritional Epidemiology
PH 2998 Special Topics in Epidemiology - Cancer Epidemiology
2 x PH 2999 Individual Study in Epidemiology

1997 (number of courses optional)

PH 9999 Dissertation Research
PH 2999 Individual Study in Epidemiology

1998 (number of courses optional)

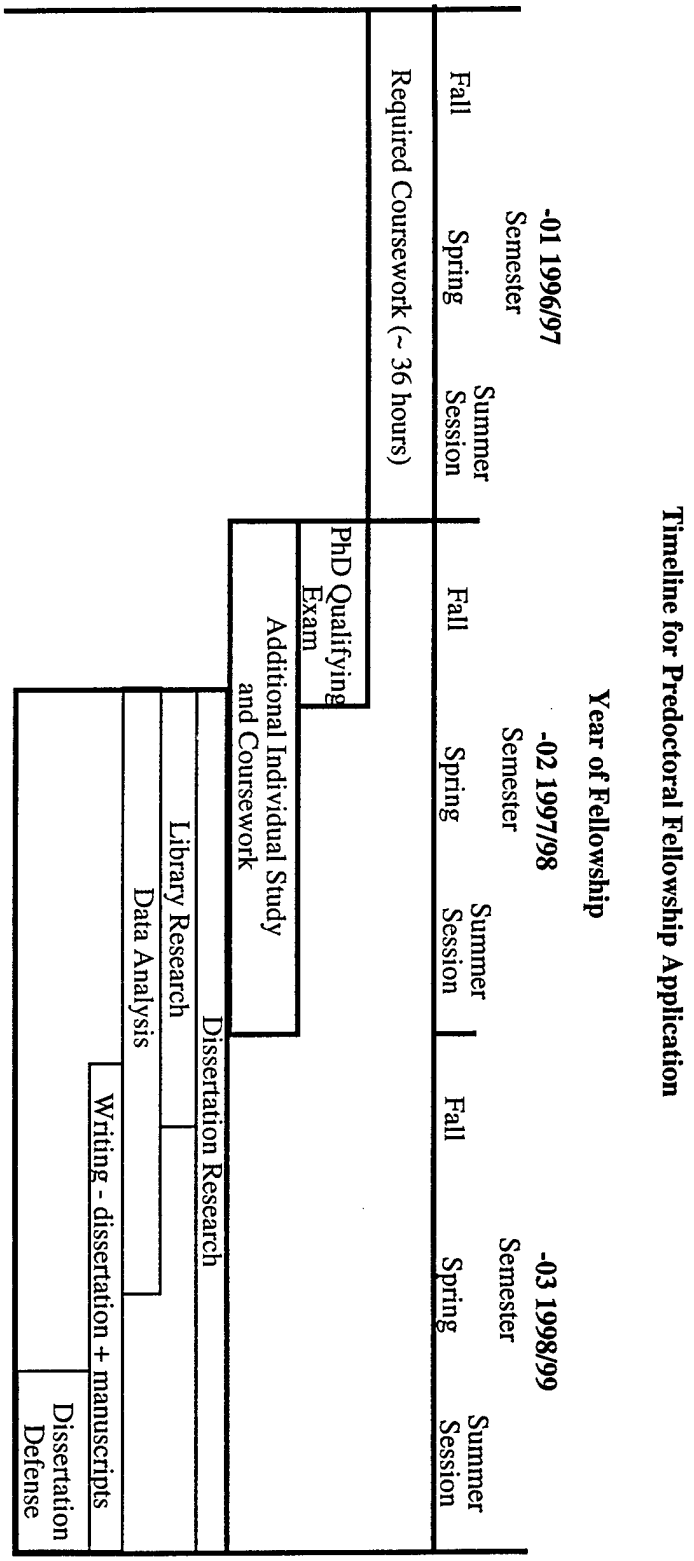
PH 9999 Dissertation Research
PH 2999 Individual Study in Epidemiology

Time-Block 2: This block represents the PhD qualifying exam which may be taken sometime during the Summer or Fall, at earliest, subsequent to completion of the proposed coursework.

Time-Block 3: The third block represents an additional year of advanced, individual study and special coursework (e.g. molecular biology and genetics) not offered at the UT School of Public Health, but at nearby institutions (e.g. Graduate School of Biomedical Sciences). This block will overlap with the fourth, which will include the initiation of library research and analysis of data from the NMWHS.

Time-Block 4: The goals of the fourth block will be to complete the dissertation, including the dissertation defense, as well as a report or published article by the end of the third year of the fellowship.

Timeline for Predoctoral Fellowship Application



Appendix A-3

- Letter Regarding Candidacy for Doctoral Degree
- List of Completed Courses
- Approval of Doctoral Thesis Committee
- UTSPH Notice of Approval to Begin Research

THE UNIVERSITY OF TEXAS
HOUSTON
HEALTH SCIENCE CENTER

School of Public Health
Office of the Dean

September 19, 1997

Kathy Baumgartner
School of Public Health
Student Mail Box

Dear Dr. Baumgartner,

Congratulations on the successful completion of your qualifying examination for the PhD degree which officially converts you from a doctoral student to a doctoral candidate.

We are pleased to have the opportunity to continue working with you as you proceed toward completion and presentation of an original research project that makes a substantial contribution to knowledge in community health sciences.

Yours sincerely,

R. Palmer Beasley, M.D.
Dean

for RPB: fg
cc: Student Records
file/comp

UT Houston School of Public Health • P.O. Box 20186 • Houston, Texas 77225 • (713) 500-9050 FAX (713) 500-9070

List of Completed Courses

1996
Applied Statistical Analysis (4)
Advanced Statistical Methods in Epidemiology - Logistic Regression (2)
Analysis of Survival Time Data (2)
Principles of Toxicology I (3)
Topics in Cancer Prevention I (1)
12 credit hours

1997
Advanced Epidemiologic Methods II (4)
Toxicology - Toxic Agents (3)
Pathology and Public Health (3)
Genetic Epidemiology (2)
Regression and Logistic Regression Analysis (4)
The Biology and Epidemiology of Cancer (2)
Molecular Epidemiology (2)
Breast Cancer: Diet and Alcohol (4)
Dissertation Research (1)
24 credit hours

1998
Dissertation Research (3)
Epidemiologic Design and Analysis(2)
Causal Inference (1)
6 credit hours

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON

SCHOOL OF PUBLIC HEALTH

REVISED COPY 3-27-98

REQUEST TO **APPOINT A Ph.D. DOCTORAL THESIS COMMITTEE**
TO BE SUBMITTED BY STUDENT'S ADVISOR

DATE 2/9/98

STUDENT'S NAME Kathy B. Baumgartner EPI

I SHOULD LIKE TO REQUEST THAT THE FOLLOWING FACULTY BE APPOINTED TO THIS STUDENT'S DOCTORAL THESIS COMMITTEE.

EPI/HSO
J. F. Annegers — Epi
FACULTY — MAJOR F

EPI/HP
R. Sue McPherson — Epid
FACULTY — MAJOR F

Biom/HP/OccH
Ralph Frankowski — Biometry
FACULTY — MINOR FIELD

Epidemiology
Field

I REQUEST THAT J. Fred Annegers CHAIR THE COMMITTEE.

ADVISOR

☑ REQUEST APPROVED

☐ REQUEST COULD NOT BE APPROVED BECAUSE _____

DEAN _____ DATE 4-17-98

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THE UNIVERSITY OF TEXAS HOUSTON HEALTH SCIENCE CENTER

The Committee for the Protection of Human Subjects

NOTICE OF APPROVAL TO BEGIN RESEARCH January 16, 1998

HSC-SPH-98-007 - "Alcohol Consumption and Breast Cancer Among Hispanic and Non-Hispanic White Women in New Mexico"
PI: Kathy Baumgartner, PhD Student; Chair - Dr. Annegers

PROVISIONS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consents, etc.

APPROVED: At a Convened Meeting

APPROVAL DATE: January 16, 1998 **EXPIRATION DATE:** December 31, 1998

CHAIRPERSON: Anne Dougherty, MD 2/4/98

Subject to any provisions noted above, you may now begin this research.

CHANGES - The P.I. must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.

INFORMED CONSENT - Informed consent must be obtained by the P.I. or designee using the format and procedures approved by the CPHS. The P.I. must instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS - The P.I. will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS - The P.I. will maintain adequate records, including signed consent documents if required, in a manner which ensures confidentiality.

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